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ORIGINAL ARTICLES

HUMORAL ANTIBODY FORMATION IN INFANTS AGED ONE TO THREE MONTHS INJECTED WITH A TRIPLE (DIPHTHERIA-TETANUS-PERTUSSIS) ALUM-PRECIPITATED ANTIGEN

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RECENT interest in the problem of the active immunization of infants under 6 months of age chiefly concerns pertussis, for in this disease early life is clearly the period of highest mortality. The immunologic problems concerned in the relationship of age to antibody formation have been discussed in the excellent reviews by Baumgartner[1] and by McKhann and Kapnick.[2]

That the newly born infant inherits from the mother little or no protection against pertussis is well known. Although attempts to immunize the infant passively by actively immunizing the pregnant mother have met with some success,[3-5] more interest has been directed toward attempts to immunize the infant actively at an earlier age than was formerly advocated. Several authors[6-12] have described the ability of young infants to form antibodies against pertussis and their findings have been supported by other workers[7,8,13,14] showing that immunization carried out at an early age either modifies or prevents the disease. In these published studies there has been considerable variation in the type of antigen used and the methods of study.

The present report describes the formation of humoral antibodies in infants immunized at 1 to 3 months of age with a triple alum-precipitated antigen containing diphtheria and tetanus toxoids and pertussis vaccine.

METHOD OF STUDY

Subjects were normal infants in regular attendance at the well baby clinic in the outpatient department of the Strong Memorial and Rochester Municipal Hospitals.

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The antigen* was alum-precipitated, consisting of a mixture of diphtheria and tetanus toxoids to which was added a suspension of Phase I, Hemophilus pertussis organisms. It contained 40 billion bacteria/cml.

The original course of immunization consisted of 3 injections of 0.5, 0.7 and 0.8 ml. of the vaccine given at 4 wk. intervals. Although it was originally planned to give the 1st injection during the 6th wk. of life, this actually occurred at various times between the 4th and 12th wk. of age.

Injection was made into the deep subcutaneous or muscular tissues of the upper arm through a 7/8 inch No. 26 gauge needle. After withdrawal of the needle the injected area was gently massaged. The 1st and 3rd injections were made into the left arm; the 2nd into the right arm. In a series of 120 injections, given by various individuals, only 4 sterile "antigenic cysts" were observed.

The schedule of injections and blood withdrawals for titration were as follows:

1 to 3 mos. of age: original course of 3 injections of vaccine at 4 wk. intervals.

4 to 6 mos. of age: (3 mos. after completion of the original course) withdrawal of 1st sample of blood for antibody titration.

7 to 9 mos. of age: (6 mos. after completion of the original course) withdrawal of 2nd blood sample for antibody titration; Schick test; a "booster" injection of 0.5 ml. of the vaccine.

8 to 10 mos. of age: (7 mos. after completion of the original course) withdrawal of 3rd sample of blood for antibody titration. In certain instances a skin test with pertussis agglutinogen was made.

In order to reduce the number of bleedings of any given infant, preimmunization samples were withdrawn from a series of 30 infants attending the same clinic. Subsequent samples from this group were not taken.

The distribution of blood samples according to the time of withdrawal after completion of the original course of immunization was as follows:

3	samples	from	each	of	18	infants	at	3, 6 and 7 mos.	after immunization
2	"	"	"	"	7	"	"	3 and 6 mos.	" "
2	"	"	"	"	10	"	"	6 and 7 mos.	" "
1	sample	"	"	"	16	"	"	3 mos.	" "
1	"	"	"	"	15	"	"	6 mos.	" "
1	"	"	"	"	9	"	"	7 mos.	" "
1	"	"	"	"	30	"	"	6 wks. to 12 mos. of age (controls)	

Titration of Blood Samples

Titrations of the serums for content of diphtheria and tetanus antitoxin were made by the E. R. Squibb Research Department, through the courtesy of Drs. A. F. Langlykke and W. E. Bunney.

Titration of Diphtheria Antitoxin

After separation of the serum from the clot, the serum was prepared for testing by 2 centrifugations, the addition of merthiolate to make a 1 to 10,000 dilution and by storage at +5°C. in the cold room.

The technic of titration, essentially that described by Volk and Bunney,[18] consisted of comparing reactions in the skin of rabbits to intracutaneous injections of serum-toxin mixtures. A few modifications as to titer tested for, dilution of medium for toxin, amount injected and reading time of the cutaneous reactions were made.

The test range for each serum was 0.001, 0.01, 0.1 and 1 u. of antitoxin. Fresh toxin dilutions were made in physiologic saline solution before each test and the optimal dilution of toxin was determined by testing mixtures of it with several dilutions of Standard N.I.H. antitoxin. The amount of the serum-toxin mixtures injected was 0.2 ml. and the reading time was 48 to 72 hrs. after injection.

Titration of Tetanus Antitoxin

The test was an adaptation of the mouse method of Glenny and Steven.[19]

Standard antitoxin (NIH; 5 u./ml.) was freshly diluted with physiologic saline solution for each test.

The test dose of Squibb toxin was determined with the standard antitoxin, which was diluted to

* Supplied by E. R. Squibb Company, New Brunswick, N.J., through the courtesy of Dr. W. E. Bunney.

contain 0.002 u./ml. Three tubes with toxin, respectively 10, 4 and 2 MLD/ml., were set up. An equal amount of antitoxin containing 0.002 u./ml. was added, making mixtures containing:

5 MLD toxin + 0.001 u. antitoxin in ml.
2 " " + " " " " "
1 " " + " " " " "

The mixtures were left standing at room temperature for 30 min. and then were injected subcutaneously at the base of the spine into 6 mice for each mixture. Swiss mice, 16 to 18 gm. in wt., were used.

It has been established that mice receiving toxin-antitoxin mixture containing 5 MLD should die in about 2 days; 50% of mice receiving toxin-antitoxin mixture containing 2 MLD should die and 50% should survive with paralysis in 4 days; mice receiving toxin-antitoxin mixture containing 1 MLD should live, some with partial paralysis in 4 days.

A similar toxin control was included with every test.

Mixtures of the unknown sera and toxin were set up using 2 MLD as a test dose.

As 0.5 ml. of the serum dilutions in the test stands for 0.001 u. of antitoxin, the serum dilution on which 50% of the mice die and 50% survive with paralysis in 4 days actually contains a 0.002 u./ml. Multiplying the units with the dilution factor gave the antitoxin content of the serum/ml.

Serum dilution 1/10; $0.002 \times 10 = 0.02$ u./ml.
" " 1/25; $0.002 \times 25 = 0.05$ u./ml.
" " 1/50; $0.002 \times 50 = 0.1$ u./ml.

Agglutinative Titers vs. Hemophilus Pertussis

Kendrick method:[17] To 0.1 ml. of the serum dilution was added 0.1 ml. of a suspension of living Phase I Hemophilus pertussis. The suspension of organisms was prepared by scraping the 48 hr. growth from the surface of Bordet medium into 1.15% solution of physiologic saline solution. The suspension was adjusted to match the turbidity of a standard suspension containing 40 billion organisms/ml. The tubes were shaken for 3 min. To each tube was added 0.4 cc. of physiologic salt solution to facilitate reading. The recorded titer was that of the last tube showing agglutination.

Flosdorf method:[18] To 0.5 ml. of the serum dilution was added 0.5 ml. of the suspension of organisms. The mixture was incubated in a water bath at 37°C. for 1 hr. and placed in the refrigerator overnight, after which the final reading was recorded. The highest dilution showing agglutination was taken as the titer.

Our modification of the above methods consisted of using a suspension of organisms containing 40 billion cells/ml. to replace that of 10 billion cells/ml. as described in the original Kendrick method and to replace that of 2 billion cells/ml. as described in the original Flosdorf method.

Slide method:[19] In this method a drop of the concentrated pertussis antigen (with dye added), prepared by the method of Powell and Jamison, was mixed with a drop of undiluted serum on the surface of a glass slide by gentle tipping of the slide. After 1 min. the reading was made by inspection of the colored material for evidence of clumping.

TABLE I

Diphtheria Antitoxin Titrations of Serums of Infants Immunized at 4 to 12 Weeks with Triple Alum-Precipitated Vaccine

Age	Total	Antitoxin u./ml. serum				
		<.01	0.1	1.0	>1.0	
<6 wks.	13	9	3	1		Controls; no injections
7–16 wks.	9	7	2			Controls; no injections
6–12 mos.	8	8				Controls; no injections
4– 7 mos.	38	1	13	17	7	3 mos. after original course of vaccine
7– 9 mos.	45		11	31	3	6 mos. after original course of vaccine
8–10 mos.	33	1		2	30	1 mo. after "booster" dose of vaccine

Results

Diphtheria: Thirty-seven (97%) of 38 infants, when tested 3 mos. after completion of the original series of injection, had 0.1 u. of antitoxin or more/ml. serum (Table I).

Six mos. after immunization, 45 (100%) in a series of 45 subjects had titers of 0.1 u. or more. At this time, as might be expected, the Schick test in each instance was negative.

One month later, after a "booster" injection of the combined antigen, 32 (97%) of 33 infants tested showed 1 u. or more of antitoxin/ml. serum.

Each of 24 (80%) in a series of 30 nonimmunized infants (controls) from 1 to 12 mos. of age, attending the same clinic, had less than 0.01 u. of antitoxin/ml. serum.

Tetanus: Thirty-six (94%) of a group of 38 titrations made 3 mos. after completion of the original course of vaccine revealed > 0.1 u. of antitoxin/ml. serum (Table II).

TABLE II

Tetanus Antitoxin Titrations of Serums of Infants Immunized at 4 to 12 Weeks of Age with Triple Alum-Precipitated Vaccine

Age	Total	Antitoxin u./ml. serum				
		<.05	.05	0.1	>0.1	
<6 wks.	13	13				Controls; no injections
7–16 wks.	9	9				Controls; no injections
6–12 mos.	8	8				Controls; no injections
4– 7 mos.	38		2		36	3 mos. after original course of vaccine
7– 8 mos.	45				45	6 mos. after original course of vaccine
8–10 mos.	34		2		32	1 mo. after "booster" dose of vaccine

Forty-five (100%) in a group of 45 tests made 6 mos. after immunization showed this level of antitoxin.

Thirty two (94%) of a group of 34, 7 mos. after the original course of injections and 1 mo. after the "booster" injection had > 0.1 u. of antitoxin/ml. serum.

Of the 30 nonimmunized infants the titer was <0.05 u./ml. of serum in each case.

Pertussis: The results of the titrations for agglutinins against Hemophilus pertussis are illustrated in Table III.

With the Kendrick method the percentage of tests with agglutinative titers of 1:320 at 3, 6 and 7 mos. after completion of the original series of injections were 0:4.4 and 11.4, respectively.

With the Flosdorf method these percentages were 22, 20 and 33, respectively.

Calculated average titers of the tests showing positive agglutinins by the tube methods give the following values:

Kendrick: 3 mos. after immunization, 1:40; 6 mos. after, 1:85, and 7 mos. after, 1:131. These values for the tests carried out by the Flosdorf method are 1:277, 1:338 and 1:374, respectively.

It is apparent from the data that practically all the control series tested by the Flosdorf method and all those tested by the Kendrick method were completely negative.

The percentage of positive tests, according to the month after immunization, made by the slide method, were: 3 mos., 53, 6 mos., 51, and 7 mos., 80, respectively. All agglutinative tests among the control groups performed by this method were negative.

Discussion

If one accepts the protective levels of antitoxin in the serum as 0.03 u./ml. in the case of diphtheria and 0.1 u./ml. for tetanus, the data obtained by the present study clearly indicate that the infants studied were satisfactorily immunized against the two diseases.

The results in the case of diphtheria are interesting, for it is generally believed that infants actively immunized while maternal immunity is still present are poor producers of

antitoxin. This view is supported by the recent observations of Cooke and associates,[20] who studied infants immunized with a combined diphtheria-tetanus alhydrox antigen.

In a group of 112 infants, 1 to 3 months of age, Cooke found that 84 (75%) had less than 0.1 unit of antitoxin per ml. of serum. Fifty (66.6%) of a group of 75 infants, injected at this age, had 0.1 unit or more of antitoxin per ml. of serum after immunization. He also found that, in a smaller group of infants possessed of passive immunity when immunized at 1 to 3 months of age, less than one third had an antitoxin level of 0.1 units

TABLE III

AGGLUTINATIVE TITERS OF SERUMS AGAINST HEMOPHILUS PERTUSSIS IN INFANTS IMMUNIZED AT 4 TO 12 WEEKS OF AGE WITH TRIPLE ALUM-PRECIPITATED VACCINE

Age	Method	Total	Agglutinative Titers: Tube Method 0	Tube Method 1:10 to 1:160	Tube Method 1:320 or>	Slide Method Total	Slide Method 0	Slide Method +	Skin Tests* Total	Skin Tests* 0	Skin Tests* +	
<6 wks.	K	13	13									Controls; no injections
	F	13	11	2		13	13	0	12	12	0	
7–16 wks.	K	9	9									Controls; no injections
	F	9	8	1		9	9	0	7	7	0	
6–12 mos.	K	8	8									Controls; no injections
	F	8	7	1		8	8	0	8	8	0	
4– 7 mos.	K	41	29	12								3 mos. after original course of vaccine
	F	27	13	8	6	41	19	22				
7– 8 mos.	K	45	28	15	2							6 mos. after original course of vaccine
	F	35	15	13	7	45	22	23	5	0	5	
8–10 mos.	K	35	14	17	4							1 mo. after "booster" dose of vaccine
	F	24	7	9	8	35	7	28	24	0	24	

K = Kendrick
F = Flosdorf
* = Agglutinogen

per ml. of serum after immunization, whereas 83% had such a titer before immunization.

In our group 16 (72%) of 22 normal infants under 4 months of age had less than 0.1 unit of antitoxin per ml. of serum, but after immunization 37 (97%) of a group of 38 infants injected at this age period had 0.1 unit or more of antitoxin per ml. of serum. This degree of protection was observed three months later and was even better one month after a "booster" injection.

Vahlquist[21] states, "The presence of antibodies in concentrations exceeding 0.1 unit per ml. inhibits the action of antigen." He further states, "Active immunization of newborn infants is feasible. The production of antitoxin is often retarded in the newborn, but the titer finally achieved is satisfactory."

It seems probable that one explanation of the discrepancy between the results described

by Cooke and those obtained by us lies in the fact that our antigen contained Hemophilus pertussis while theirs did not. Support of this explanation is to be found in the recent paper by Bell[22] who compared the antigenic potency of an unmixed alum-precipitated toxoid with a similar one mixed with Hemophilus pertussis vaccine. Bell concluded in part, "The routine use of an alum-precipitated mixture of diphtheria toxoid and pertussis vaccine as prepared for this study and given in two doses with a four-week interval between doses to young children in Norfolk, Va., and a similar community, not only should result in a better protection against diphtheria, as measured by the Schick test, than that which would result from the similar use of ordinary unmixed alum-precipitated diphtheria toxoid, but also should be effective for diphtheria immunization when given to infants 2-to-5 months of age."

The results of our study concerning protection against pertussis are not easily interpreted. It is apparent (Table III) that few of the immunized infants developed titers of 1:320 or greater, the level which has been suggested to indicate lack of susceptibility.

Miller[23] observed a group of immunized children subjected to family exposures in whom the serum agglutinative titers were known. Of 83 such cases, 12 developed pertussis. In each of these 12 children a titer of 1:160 or lower existed; four of them had no demonstrable agglutinins. Among the 71 who escaped the disease, 47 had titers of 1:320 or higher, while 24 had titers of 1:160 or lower; three had no agglutinins. In other words, the secondary attack rate among those with titers of 1:320 or higher was 0, while among those with lower titers or none at all, the attack rate was 33%.

Sako,[24] also studied the relationship between clinical immunity and the serum agglutinin titer. His findings in a study of household exposures among immunized infants and children are summarized as follows:

Serum titers	No. of cases	Percentage attacked
1:320	149	0
1:160	53	11.3
1: 40	91	18.7
0	27	33.3

Sako found that among the controls (nonimmunized) with 0 titers the attack rate was 89.7%.

If we assume that the members of our series with titers of 1:320 or higher are completely protected and that 33% of these with titers of 1:160 or lower would develop the disease upon exposure, it is possible to analyze the results in terms of the number of cases of pertussis that might be expected to develop, if the infants were subjected to family exposure. In this calculation the titer values obtained by the Flosdorf method are used, for this method gives results more nearly in accord with those obtained by the Miller and Silverberg[25] method used by Miller and Sako.

	Total tested	No. with titers 1:160 or lower	Expected no. of pertussis attacks
3 mos. after immunization	27	21	7
6 " " "	35	28	9
7 " " "	24	16	5
NONIMMUNIZED (controls) with negative titers.	26		23

Thus, if to this series is applied what information is available from the studies of Miller and Sako concerning the relationship of serum agglutinin titer to protection, we may estimate that roughly one fourth of the immunized infants would develop pertussis, if exposed to family contacts. This actually indicates significant protection, for, under these circumstances, epidemiologists agree that from 75 to 90% of them, if they were nonimmunized, would develop the disease.

It is of interest and perhaps significant that the skin test* (Flosdorf) performed on 27 of the nonimmunized infants was negative in each case, while in 29 of the immunized group tested six and seven months after completion of the original course of injections it was positive. In nine infants who had failed to develop demonstrable agglutinin titers, the test was positive, a finding which suggests that further investigation may prove the skin test to be a sharper indication of clinical immunity than is the agglutinative reaction.

Conclusion

Immunization of infants, 1 to 3 months of age, with an alum-precipitated antigen containing diphtheria and tetanus toxoids and Hemophilus pertussis organisms resulted in satisfactory humoral antibody levels against diphtheria and tetanus. Ninety-seven per cent of the subjects tested revealed more than the generally accepted level of protection against diphtheria and 94% showed a similar result against tetanus.

In regard to pertussis, only a few of the immunized infants developed agglutinative titers of 1:320 or higher. However, analysis of the titers in terms of the expected number of cases of pertussis, if subjected to family exposure, indicates that probably 75% of the infants were protected.

When tested six months after the completion of the original series of injections, each of 29 infants gave positive skin reactions to the injection of agglutinogen.

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SPANISH ABSTRACT

Formación de Anticuerpo Homoral en Infantes de Uno a Tres Meses de Edad Inyectados con un Antígeno Alum-Precipitado Triple (Difteria-Tétano-Pertusis)

La inmunización de infantes de 1 a 3 meses con un antígeno alum-precipitado conteniendo difteria y toxoides de tétano y organismos de pertusis hemofílicos resultó en niveles de anticuerpo humoral satisfactorios contra difteria y tétano. Noventa y siete por ciento de los sujetos analizados revelaron más del nivel de protección generalmente aceptado contra difteria y 94% mostraron un resultado similar contra el tétano.

Con respecto a la pertusis, solamente unos pocos de los infantes inmunizados desarrollaron títulos de 1:320 o más altos. Sin embargo, el análisis de los títulos en términos del número de casos de pertussis esperado, si sujetos a la exposición de familia, indica que probablemente el 75% de los infantes estaban protegidos.

Cuando analizados seis meses después de completar las series de inyecciones originales, cada uno de los 29 infantes dió reacciones de piel positiva a la inyección de aglutinógeno.

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FATAL BORIC ACID POISONING IN A NEWBORN INFANT

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BORIC acid, although of doubtful therapeutic value, is used widely in a large variety of conditions. It is a lethal agent and responsible for many unnecessary fatalities. Deaths have been reported following the ingestion of boric acid, its application to lesions of the skin and mucous membrane, its installation into serous cavities and its administration parenterally. Cases have been reviewed by McNally and Rust,[1] McNally and Ruckstinat,[2] Ross and Conway[3] and Watson,[4] with comments on the dangers inherent in the use of boric acid and borates in powder, crystal, ointment or solution forms. Experimental studies on the toxic effects of boric acid ointment in the treatment of burns have been reported by Pfeiffer, Hallman and Gersh.[5] In spite of repeated warnings as to the careless use of boric acid,[6,7] fatalities still occur.

The following report of the death of a newborn infant from boric acid is an example.

CASE REPORT

S. S., female, white, was born normally, full term, wt. 3825 gm. Feedings of diluted evaporated milk were given. The early postnatal course was uneventful except for the occurrence of several loose green stools on the day of discharge to home. Twenty-four hours later, she regurgitated. The stools were loose and frequent; no blood was seen. The buttocks became reddened and excoriated. The mother applied daily to the gluteal areas unknown amounts of boric acid ointment, U. S. P. 10%, and dusted liberal quantities of boric acid powder daily onto the baby's diapers.

The symptoms became aggravated and on the 8th day of life the infant was brought back to the hospital, acutely ill and dehydrated. Signs of an early bronchopneumonia were present. Death took place 12 hours later.

Postmortem Examination (Dr. Thomas A. Gonzales, Chief Medical Examiner, New York City).—Gross Pathology: Skin over the baby's right shoulder showed a bullous lesion about 2.5 cm. in diameter with the edges still adherent. A similar bleb was on the left arm near the shoulder. A denuded area 9 cm. in diameter involved the skin of the vulval, anal and surrounding regions. Brain was congested. Liver was a finger's breadth below the costal margin. It was congested and on section presented light brown mottled areas in a dark red-brown matrix. Upper part of the small intestine midway to the ileum showed no lesions. From here down to an edematous and hemorrhagic ileocecal valve, there was congestion and superficial necrosis of the mucosa. Hemorrhage and necrosis were prominent in the large gut.

Lung surfaces and parenchyma were engorged and had small areas of mottled pink and gray. Bronchi and pulmonary vessels were congested. Kidney capsules stripped easily, leaving smooth, lobulated surfaces. On section, the upper halves of both kidneys had hemorrhages into the cortex and medulla. The remainder of the kidneys, the kidney pelves and the urinary bladder showed congestion only. The latter contained some cloudy yellow urine.

The other organs showed nothing unusual grossly.

Microscopic Pathology: The lungs were congested and had small foci of bronchopneumonia. Other areas exhibited thickening of the areolar septa. Liver parenchyma showed lipoid and granular degenerative changes. Kupfer cells were normal. Kidneys presented advanced nephrotic changes, with hemorrhages into the interstitial tissues of the cortex and medulla. Convoluted tubules showed granu-

From the Bureau of Preventable Diseases, Department of Health, New York, N.Y.
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lar degeneration, some cells containing detritus. Urinary bladder wall showed edema with spotty hemorrhages. Mucosa was well preserved. Mucosa and submucosa of the lower ileum were infiltrated with leucocytes and round cells. Pseudomembranous deposits were on the mucosal surfaces. Blood vessels of the small gut were engorged. Large intestine showed a similar pseudomembranous colitis and engorgement of blood vessels. In some areas, the epithelial cells of the tubular glands had disappeared, leaving superficial ulcerations of the mucosa. Brain cortex, basal ganglia, brain stem and cerebellum showed congestions. Spleen and the adrenal glands were similarly engorged.

Bacteriology: Postmortem cultures from the gut and the spleen were negative for pathogenic bacteria.

The history of the use of boric acid in ointment form and as a dusting powder, the excoriated buttocks, the diarrhea and dehydration, the presence of bullous skin lesions, and the hemorrhagic phenomena seen in the kidneys and intestines suggested the possibility of boric acid poisoning to Dr. Gonzales.[8] Fresh specimens of the gut and liver, and pieces of the brain, liver, and kidneys preserved in formaldehyde were sent to Dr. Alexander Gettler, Principal Chemist, Chief Medical Examiner's Office, for chemical analysis.[9] Boric acid was found in the amount of 26 mg. in 50 gm. of composite sample, or 0.052%. In the opinion of Dr. Gettler, this quantity represents a lethal concentration of boric acid.

Discussion

Since the organ samples were pooled for chemical analysis, no true comparison can be made with the few available assays for boric acid made on individual organs in fatal cases. An idea of the values that have been stated as representing toxic concentrations can be had from the investigations of McNally and Rust.[1] In six newborn infants averaging 3200 gm. in weight, the greatest accumulations of boric acid were found in the brain, 0.210%, the liver, 0.182%, and the bowel, 0.102%. Lesser amounts were recovered from the heart, lungs, stomach and kidneys, with percentages of 0.085, 0.0516, 0.0271, and 0.0124, respectively. McNally and Ruckstinat[2] subsequently assayed the organs of two additional newborn infants who died from boric acid poisoning. The livers showed 0.028 and 0.001% boric acid, the bowels 0.010 and 0.056% and the kidneys 0.100 and 0.130%.

The amount of boron ordinarily present in the human body is not known. Using a color method, Muscati[10] found traces of boron in the organs of two human fetuses and in those of a 27 year old male who died suddenly from pericarditis. According to Calvery,[11] boron is a nonnutritive, nontoxic trace element in man, the quantity being related to that ingested in food. Boron is widely distributed in plant tissues where it plays a significant rôle in normal metabolism. Analysis of foodstuff has shown an average boron content of 10 ppm. No such function has been demonstrated for boron in mammals.

The absorption of boric acid and its diffusion in the body are rapid. An idea of this rate may be had from the experiments of Kahlenberg.[12] After immersing his feet with intact integument in a warm mixture of 450 gm. of boric acid in 6 l. of water and 3 l. of 95% alcohol, he was able to detect boric acid in the urine in 20 minutes. This result could not be repeated with the sodium or lithium salts of boric acid. Pfeiffer, Hallman and Gersh[5] could not detect the presence of boric acid in the urine when a 5% aqueous solution, or the ointment, was applied to the intact human skin.

With the absorption of toxic amounts of boric acid, symptoms referable to the gastrointestinal tract occur, such as salivation, nausea, persistent vomiting, colic-like pains in the abdomen and diarrhea. Subnormal temperature, circulatory depression, shock and coma ensue. Death is due to vascular collapse and central nervous system intoxication with respiratory failure.[8,13,14] In addition, the skin may show bullous lesions or eczema-like eruptions with a patchy exfoliation. A scarlatiniform or "boiled lobster" rash has also

been noted, with subsequent desquamation on recovery. This process may extend to include the mucous membranes.[4] A grayish line similar to that seen in lead poisoning has been described. Albumin and casts are found in the urine. A tubular degeneration of the kidneys is seen at postmortem examination. The liver is only slightly affected. The amount of boric acid and the blood levels that will produce toxic symptoms in man are not definitely known. Nor has accurate determination been made of the fatal dose that is variously estimated from 15 to 30 gm. in adults and from 3 to 6 gm. in infants.[8,13,14]

Excretion of boric acid in the urine begins early. Grollman and Slaughter[13] state that one half is excreted in 12 hours. The remainder is eliminated slowly, traces being found in the urine as long as five days later. Cope[15] analyzed the urine of 20 patients who were being treated for extensive burns. The patients maintained normal kidney function. A maximum of 2 gm. of boric acid were excreted in the first 24 hours. When boric acid solution was used to irrigate granulating wounds, as much as 2.5 gm. were excreted in the urine in 24 hours. The ease with which boric acid is absorbed through injured skin or mucous membranes is readily seen.

Boric acid is not a mild and harmless drug. It is quickly absorbed into the body and, in proper amounts, may readily cause toxicity and death. In addition, boric acid exhibits a selective affinity for certain organs, such as the brain and spinal cord. When consideration is given to the extensive use of boric acid in various forms, it is surprising that more instances of poisoning have not been reported. It is possible that many cases have occurred unsuspected. Furthermore, the number of deaths from boric acid poisoning is fortunately low. These deaths may represent examples of hypersensitivity to the chemical. Nevertheless, the fatalities are needless. The doubtful benefits that are derived therapeutically from boric acid hardly justify its continued use, particularly when many more effective drugs are available.

Summary

A case is reported of a 9 day old baby who died from boric acid poisoning. The chemical was applied as an ointment to a large excoriated area of the baby's buttocks and as a powder on the diapers.

It is suggested that boric acid should be discarded in medical practice, since its potential toxicity represents a hazard that is out of proportion to the doubtful therapeutic value of the drug. Boric acid has been outmoded by more effective modern medications.

Acknowledgment

Assistance in the preparation of this paper was given by Dr. Thomas Gonzales, Chief Medical Examiner, Dr. Alexander Gettler, Principal Chemist, Chief Medical Examiner's Office, and Dr. Morris Greenberg, Director, Bureau of Preventable Diseases, Department of Health, New York City.

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SPANISH ABSTRACT

Fatal Envenamiento con Ácido Bórico en un Recién-Nacido

Se relata un caso de un bebé de 9 días edad que murió de envenamiento de ácido bórico. Esta sustancia química fué aplicada como una pomada en una area excoriada de las nalgas del bebé y como polvo en los pañales.

El caso fué de diarrea y deshidratación y lesiones ampolladas de la piel. El exámen después de la muerte mostró hemorragias en los riñones e intestinos. Se analizaron espécimenes frescos del intestino y del hígado y pedazos del cerebro, hígado y riñones que se conservaron en formaldehido.

Se encontró el ácido bórico en la cantidad de 26 mg. en 50 grn. de la muestra, o 0.052%. Esta cantidad representa una concentración letal de ácido bórico en los tejidos.

Se sugiere que se descarte el ácido bórico de la práctica médica, ya que su toxicidad representa un peligro que está fuera de proporción al valor terapéutico dudoso de la droga. El ácido bórico ha sido substituído por medicamentos modernos más eficaces.

145 East 61st Street

VARIABLE RESPONSE TO VITAMIN B_{12} OF MEGALOBLASTIC ANEMIA OF INFANCY

By CALVIN W. WOODRUFF, M.D., HOWARD W. RIPY, M.D., J. CYRIL PETERSON, M.D., AND WILLIAM J. DARBY, M.D., Ph.D.
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THE term "megaloblastic anemia" has been used by Zuelzer and Ogden[1] to designate a normocytic or macrocytic anemia occurring in infancy and childhood and characterized by a megaloblastic arrest of the bone marrow. The disease responds to liver extract or to pteroylglutamic acid (folic acid).

The clear differentiation of this syndrome followed the discovery of potent hematopoietic agents, the development of simple technics for the study of bone marrow, and their application to the routine study of anemias of childhood. While others had previously described macrocytic anemias probably belonging in this group, the first certain cases were reported by Faber[2] in 1928. Faber described three unusual cases of macrocytic anemia, two of which responded to liver extract. Several similar cases were soon reported.[3] The discovery of pteroylglutamic acid, a compound of known chemical structure and effective in the treatment of macrocytic anemias, has stimulated further clarification of this particular anemia.[1]

The recent isolation from liver[4,5] of another hematopoietic substance, vitamin B_{12}, and the demonstration of its effectiveness in the treatment of pernicious anemia[5,6] provide an additional tool for the study of megaloblastic anemia. The available information[7,8] indicates that one μg. of B_{12} possesses the hemapoietic activity in pernicious anemia of approximately one U.S.P. unit of purified liver extract. A single dose of 25 μg. will usually be followed by a maximal reticulocytosis in pernicious anemia.[7] The case reports to follow illustrate the variability of response in megaloblastic anemia to vitamin B_{12};* two patients showed excellent responses while a third patient showed no hematologic response. The latter patient subsequently responded well to folic acid.

CASE REPORTS

Case 1. C. H., a 17 mo. old white infant boy, was admitted to Vanderbilt University Hospital with the complaints of pallor and swelling of the legs. He had been breast-fed since birth with supplements of small amounts of oatmeal, potatoes and, occasionally, small quantities of tomato juice. Seven weeks before admission he developed a sore mouth, "thrush" and diarrhea. He was treated at home with penicillin and "large" amounts of riboflavin with pronounced improvement. Beginning 2 wks. before admission he gradually developed a massive dependent edema and increasing pallor. Two days before admission he was noted to have a "cold." On examination the whole body, especially the dependent portions, was markedly edematous. There was a lemon yellow tint to the skin and the mucous membranes were extremely pale. Both corners of the mouth were cracked and reddened;

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tongue was slick and moderately red. Abdomen was protuberant with a questionable fluid wave. Liver was barely palpable and the spleen was not felt. Musculature was weak and atrophic. The remainder of the physical examination was essentially normal. Hematologic data are given in Figure 1. Laboratory findings were as follows: total serum protein, 3.1 gm./100 ml.; albumin, 2.1 gm./100 ml.; nonprotein nitrogen, 20 mg./100 ml. Urinalysis was normal. Stool contained no occult blood. Fasting serum vitamin C was 0.3 mg./100 ml. and rose to 2.0 mg./100 ml. 4 hrs. following the intramuscular injection of ascorbic acid 200 mg. Cephalin flocculation test was ± at 48 hrs. and the thymol turbidity was 6.5 u. Roentgen examination of the chest and long bones was not remarkable. Sternal aspiration revealed megaloblastic marrow with rare megakaryocytes and platelets. Numerous neutrophils with hypersegmented nuclei were also seen.

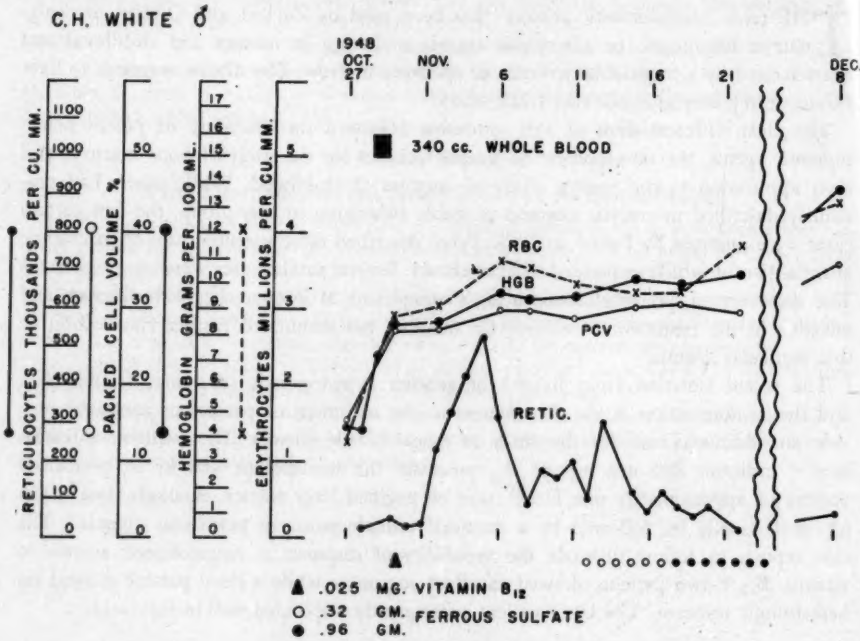

FIG. 1. Case 1. Hematologic response of patient with megaloblastic anemia to administration of vitamin B_{12}.

He was immediately given 3 transfusions totaling 340 ml. of whole blood and 5 ml. of concentrated, salt-free human serum albumin intravenously. He was offered whole cow's milk and a soft diet, and given a multivitamin preparation.* Medicinal iron was withheld. On the 4th hospital day vitamin B_{12} .025 mg. was given intramuscularly. A profuse diuresis followed the administration of repeated small amounts of serum albumin intravenously and his extreme emaciation became more apparent. On the 8th hospital day he developed a bronchopneumonia which responded to penicillin therapy. Cheilosis and glossitis disappeared and the serum proteins returned to normal levels. He ate poorly until the 13th hospital day, when he developed a voracious appetite, became interested in his surroundings and began to gain wt. Sternal aspiration on the 16th day revealed an increase in the number of normoblasts although a few earlier forms were still present. Gastric analysis before discharge revealed free acid only after histamine stimulation.

* Mead Johnson's Polyvitamin Dispersion®, containing vitamins A and D and thiamine, riboflavin, niacin amide and ascorbic acid.

When last seen in the outpatient department, he was continuing to thrive at home. Examination of his blood at that time showed essentially normal values.

Case 2. C. S., a white boy, was born here at Vanderbilt University Hospital. Efforts at breast feeding were unsuccessful and he was placed on an evaporated milk formula which was changed at 2 mos. to a goat's milk formula.* At 3 mos. of age he began taking undiluted pasteurized goat's milk. Small amounts of vegetables and cereal were given beginning at the age of 6 mos. Custard, fruits and egg yolk were later taken in reasonable amounts. Six drops of navitol and 50 mg. of ascorbic acid or 3 to 4 oz. of orange juice daily were given regularly from birth.

He was seen again at the age of 9 mos. because of severe diarrhea, fever and vomiting for 6 days following a mild diarrhea of 3 mos.' duration. He was dehydrated and acidotic. Examination revealed otitis media and pharyngitis. Ps. aeruginosa was the only abnormal organism found in the stools. Blood picture following rehydration is presented as the initial points in Figure 2. He improved with

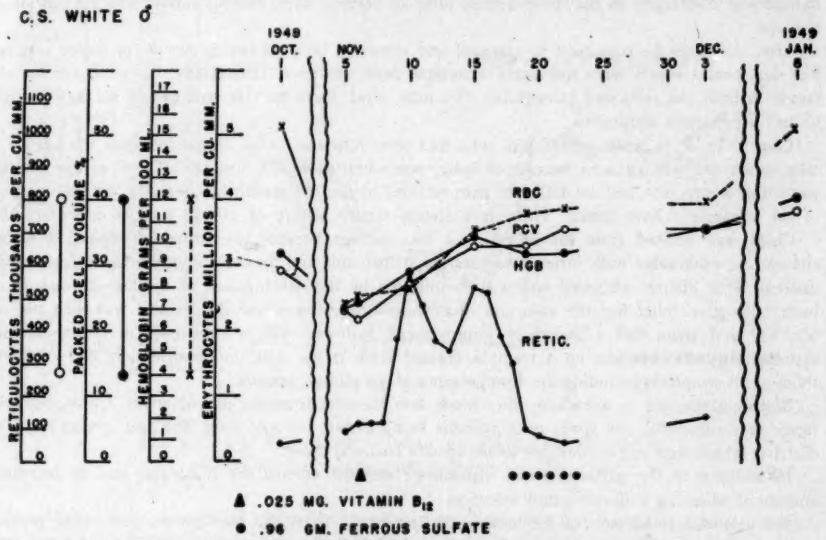

FIG. 2. Case 2. Hematologic response of patient with megaloblastic anemia to administration of vitamin B_{12}.

sulfadiazine therapy and was given ferrous sulfate, 0.26 gm. daily, and a B-complex preparation.† Bone marrow examination was not made. He was discharged much improved after 10 days.

During the following 3 wks. he was seen repeatedly as an outpatient. He continued to have recurrent episodes of diarrhea and a persistent respiratory infection. Appetite was extremely poor. Salmonella organisms were cultured from the stools on 1 occasion. Diarrhea failed to respond to starvation and sulfonamide therapy and, at the age of 10 mos., he was readmitted to the hospital for the 3rd time. Examination revealed a pale, irritable, moderately dehydrated, afebrile infant. No evidence of infection was found. No glossitis, jaundice or splenomegaly were noted.

Hematologic findings are presented in Figure 2.

Laboratory data were as follows: total serum protein, 6.5 gm./100 cc.; serum albumin, 4.6 gm./100 cc.; NPN, 27 mg./100 cc.; CO_2, 18.9 mEq./l.; serum calcium, 10.8 mg./100 cc.; serum phosphorus, 4.0 mg./100 cc. Urine was normal. Sternal marrow aspiration 2 days after admission revealed megaloblastic marrow and hypersegmentation of the polymorphonuclear neutrophils. The next day the fasting serum ascorbic acid was 0.1 mg./100 cc. A vitamin C saturation test 4 days later showed a fasting value of 0.00 mg./100 cc. and 1.3 mg./100 cc. 4 hrs. following the administra-

* The reason for this change was that the father was employed at a goat dairy.

† A hospital preparation containing thiamine, riboflavin and niacin only.

tion of 200 mg. of ascorbic acid intramuscularly. Tryptic ferments were present in the stool. Roentgen examination of the long bones revealed no significant changes.

Patient was placed on a diet of evaporated goat's milk without supplementation. He was given vitamin B_{12} 0.025 mg. subcutaneously. Three days later the diet was changed to whole cow's milk because he had refused the evaporated goat's milk. Two days later the sternal marrow showed normoblastic erythroid elements and was otherwise normal.

He continued to do poorly on the restricted diet. He did not rest well or show much interest in his surroundings until 11 days after the injection of vitamin B_{12}. At about this time he regained his appetite and his irritability and apathy were gradually replaced by happier interest in his surroundings. Soft foods, a polyvitamin dispersion* and ferrous sulfate (0.26 gm. 3 times a day) were begun 12 days after the administration of B_{12}. Two attempts at gastric analysis at this time yielded extremely small amounts of gastric fluid, neither of which contained free acid after histamine. Patient was discharged on the above regime after 20 hospital days. Ferrous sulfate was not continued at home.

After discharge he continued to eat well and remained in good health except for minor respiratory infections, which were not again associated with diarrhea. Hemogram showed a further increase in both red cells and hemoglobin 1½ mos. after discharge. He had gained 2.2 kg., though he had a persistent rhinorrhea.

Case 3. H. P., a white infant girl, who had been followed as an outpatient from the age of 5 wks. when she was 1st seen because of colic, was admitted to the hospital at 1 yr. of age. In the preceding 3 mos. she had 1st failed to gain wt. and in the last month had actually lost wt. in spite of an adequate caloric intake. There is a strong family history of allergy on the maternal side.

Child was weaned from the breast at 2 wks. of age because the mother developed a breast abscess. An evaporated milk formula was started at that time and the child immediately began to have distress. This distress persisted and was complicated by the development of eczema. A formula of buttermilk gave relief but the rash and distress recurred after a few days. Child was then put on Mul-Soy and again had a period of improvement, followed with a recurrence of the abdominal distress. She was then put on a formula derived from goat's milk and immediately had complete relief of all symptoms including the disappearance of the allergic eczema.

Mother attempted to introduce other foods into the diet from the age of about 2 mos. but was never very successful, the goat's milk formula being almost the sole food. She had several bouts of diarrhea which were not attributable to any specific bacterial cause.

In addition to the gastrointestinal disturbance and the eczema the child also had an increased amount of wheezing with respiratory infection.

She was seen at 10 mos. of age because of irritability. There had been no wt. gain in the preceding 2 mos. At this time her blood picture showed RBC 3.62 million/cmm., with Hgb. 10.5 gm./100 cc., WBC 10.6 thousand/cmm. with a normal differential except for a 7% eosinophilia. In the next month the child showed increasing irritability and apathy. She had continued to take a fair amount of milk, enough to supply her caloric needs, but in spite of this lost 0.5 kg. in wt. without having any respiratory infection or gastrointestinal disturbance except the passage of 3 to 5 loose stools a day.

On her last admission at 1 yr. of age she appeared pale, listless and apathetic. Her only response was to whine. She sucked her fingers constantly. Examination revealed no significant physical abnormality. Skin was clear and respiratory tract was normal. Blood findings are shown in Figure 3. Other laboratory data were as follows: Kahn, negative; NPN, 37 mg./100 cc.; fasting sugar, 113 mg./100 cc.; chlorides, 101 mEq./l. and CO_2 combining power 26.8 mEq./l. A glucose tolerance test showed levels of 102, 89, 95, 85, 88 and 76 mg. at fasting, 1, 2, 3, 4 and 5 hrs., respectively. Vitamin A absorption test showed a fasting level of 84 I. U. and a 4 hr. level of 82 I. U. Free hydrochloric acid was present on gastric analysis. Microscopic examination of the stools revealed an increased amount of fat, absence of starch, even after a test meal with starch, and normal tryptic enzymes. Tuberculin and histoplasmin tests were negative. Cultures revealed a normal throat flora, sterile blood and sterile urine cultures, and from the colon atypical organisms, not strictly classifiable but probably belonging to the Pr. morgani group, were recovered on several occasions. Fluoroscopy of the small intestine showed an abnormal segmentation pattern.

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* Mead Johnson's Polyvitamin Dispersion®, containing vitamins A and D and thiamine, riboflavin, niacin amide and ascorbic acid.

Patient was maintained on a diet essentially the same as she had at home: a basic diet of evaporated goat's milk with protein hydrolysates 60 gm. added daily. She was offered oatmeal, pureed fruits and vegetables, but these were almost entirely refused. Vitamin intake was maintained by a teaspoonful of polyvitamin dispersion* daily. Formula was given by gavage. Stools were loose but usually not increased in number.

The impression was that the patient had a mild celiac reaction, probably based on gastrointestinal allergy.

The studies mentioned were carried out over a period of 1 wk. and had included the withdrawal of a considerable amount of blood from the patient. Nine days after admission Hgb. had fallen to 7 gm./100 cc. and RBC was 2.68 million/cmm.; 2 days later the values were 6.5 gm./100 cc. and

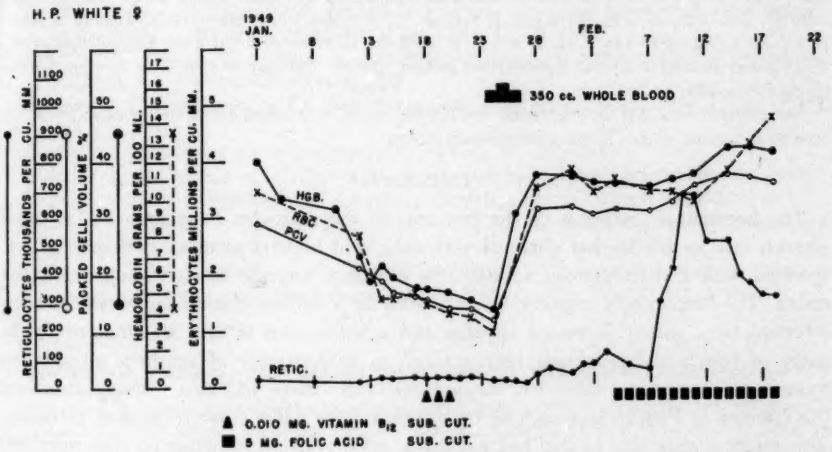

FIG. 3. Case 3. This patient failed to respond to administration of vitamin B_{12} but subsequently responded to folic acid.

1.75 million/cmm., respectively. Sternal marrow showed at this time a definite megaloblastic maturation arrest, with 28% megaloblasts. During the next 5 days on the same regime there was a further decrease in red cells to 1.65 million/cmm. and in Hgb. to 5.2 gm./100 cc. The reticulocytes throughout had been in the neighborhood of 2% or 25,000 to 30,000/cmm. Granulocytes were not significantly depressed and there was no leucopenia, but the platelets were relatively decreased. Thirty μg of vitamin B_{12} was administered parenterally in divided doses on the 14th, 15th and 16th days after admission and the patient's blood was observed at intervals thereafter. Hgb. level fell progressively to 4.1 gm./100 cc. and RBC to .96 million/cmm. At this point she became febrile due to a Staph. aureus septicemia which had developed in spite of the fact that she was receiving penicillin 25,000 u. every 3 hrs. WBC with this infection was 11 thousand/cmm. Infection was controlled by changing from penicillin to streptomycin. It was also essential to give blood transfusions. On the 8th day after the 1st administration of vitamin B_{12} she was given a series of whole blood transfusions totalling 350 cc., enough to raise her Hgb. level to 11.2 gm./100 cc. and RBC to 3.49 million/cmm. Following the transfusion there was a slight increase in the number of reticulocytes to a peak of 112,000/cmm. This temporary rise was not sustained and after a few days the level fell to 51,000/cmm. This seemed to denote a complete failure of the vitamin B_{12} to bring about a remission in the patient's anemia. The slight response which did occur could be attributed entirely to the blood transfusions. That the hematologic defect was not significantly improved by B_{12} was further reflected in the marrow which at this time showed 15.5% megaloblasts and only 2% normoblasts despite the transfusion.

* Mead Johnson's Polyvitamin Dispersion®, containing vitamins A and D and thiamine, riboflavin, niacin amide and ascorbic acid.

Some general improvement in her condition occurred following the blood transfusions and vitamin B_{12}: there was improvement in her environmental reactions and she was more attentive and happy, though far from normal.

She was started on folic acid, 5 mg. intramuscularly daily, 1 mo. after admission. Two days later she developed a moderately severe acute upper respiratory infection and ran for several days a temperature of 38.8° C. In spite of this infection there developed on the 4th day after the initiation of folic therapy a reticulocytosis of 8% which increased rapidly in the next 3 days to a level of 20.7% or 664,000/cmm. This was associated with great improvement in the patient's general condition as well as a remission from the anemia and the megaloblastic arrest. For the 1st time during her hospital stay she began to take food when it was offered. Tolerance curves for glucose and vitamin A run 13 days after folic acid showed considerable change from the initial curves. Blood glucose values were 89, 100, 125, 96, and 111 mg.% at fasting, ½, 1, 2 and 3 hrs., respectively. Vitamin A levels rose from a fasting of 163 I. U. to 473 I. U. at 4 hrs. after an oral test dose. Fluoroscopy of the small bowel showed a normal segmentation pattern. On the 14th day of folic acid therapy she was taking food avidly.

She changed to a diet of evaporated cow's milk, meats, vegetables, fruits and cereals. There has been no recurrence of the allergic gastroenteritis to date.

Discussion

The hematologic response of the first two of these patients to vitamin B_{12} is in all respects comparable to that obtained with folic acid or liver extracts. Both patients responded with a reticulocytosis followed by a prompt increase in circulating blood elements. The hematologic response was followed by a definite clinical improvement characterized by a greatly increased appetite and a willingness to take all kinds of foods, many of which had previously been refused, a disappearance of apathetic attitude, an increase in activity and other less tangible reactions. There was also a disappearance of the diarrhea in Patient 2, though he continued to have a low grade respiratory infection. This might suggest that he had had a minimal celiac reaction, although no tests were performed which would establish or exclude this possibility.

The response of the first two infants was typical of a remission induced by an active hemopoietic agent. While it is to be admitted that the interpretation of a specific response to vitamin B_{12} is complicated by the possible effect of the initial transfusion, Case 2 was uncomplicated by such supportive therapy. In view of the similarity of the courses of the two infants, it would seem that both remissions were due to the administered vitamin B_{12}.

While the failure of vitamin B_{12} to induce a remission in Case 3 might be attributed to the septicemia which developed, it is noteworthy that the subsequent response to folic acid was not inhibited by the moderately severe respiratory infection. Again, one may hold that the effect of the latter agent was conditioned by the transfusions, but it is obvious that the transfusions were not followed by significant reticulocytosis, erythropoiesis or marrow changes until folic acid was given. It is believed that the response of Patient 3 was to folic acid after failure of vitamin B_{12} to promote erythropoiesis.

If this interpretation is correct, it implies that the megaloblastic anemia of infancy may not be a single entity, but, rather, a syndrome, some cases of which may respond to one of the newer hemopoietic vitamins while other cases respond to another. The relationship between these two factors is as yet obscure.

Summary

Two cases of megaloblastic anemia in infancy have improved following treatment with vitamin B_{12}. A third case failed to respond to this factor but subsequently responded to

pteroylglutamic acid (folic acid). It is suggested that megaloblastic anemia may be a syndrome which embraces more than one entity.

Addendum

Two additional patients with megaloblastic anemia have been treated with vitamin B_{12}. One responded to this therapy and the other did not. The latter then experienced a remission when folic acid was given.

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Spanish Abstract

Respuesta Variable a la Vitamina B_{12} de Anemia Megaloblástica de Infancia

Tres casos de anemia megaloblástica de infancia fueron tratados con Vitamina B_{12}. Los dos primeros pacientes mejoraron después del tratamiento y el patrón similar de respuesta en ambos de ellos fué sugestivo de una remisión inducida por un agente hematopoyético activo. Esta respuesta fué en todo sentido comparable a la que se obtuvo con ácido fólico o extractos de hígado y fué acompañada por un mejoramiento clínico caracterizado por un aumento grande del apetito, desaparecimiento de actitud apática, aumento de actividad y otras reacciones menos tangibles. El tercer paciente dejó de responder a la vitamina B_{12}. Este paciente tuvo una reacción celíaca marcada. El hecho de que este fracaso no dependió de la septicemia que se desarrolló, se nota porque el paciente más tarde respondió al ácido fólico a pesar de una infección respiratoria moderadamente severa.

Estas observaciones denotan que la anemia megaloblástica de infancia no puede ser una entidad sino que más bien un síndroma, algunos de cuyos casos pueden responder a una de las vitaminas hemopoyéticas más nuevas, mientras que otros casos responden a otra. La relación entre estos dos factores permanece oscura todavía.

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UNUSUAL SYNDROME ASSOCIATED WITH CANDIDA ALBICANS INFECTION

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FOUR cases of infection with Candida albicans (monilia), three of which presented an unusual clinical syndrome, were reported by Schultz in 1935.[1,2] These children had a focus of fungus infection in their mouths and gastrointestinal tracts associated with dwarfing, alopecia, paronychia and repeated eruptions involving the face, perineum, perirectal area, neck and extremities.

A review of the literature[1-34] reveals 40 cases of generalized or systemic C. albicans infection associated with a similar focus in the mouth or gastrointestinal tract. These cases are differentiated from those in which the infection is localized or where it is systemic with primarily pulmonary or endocardial involvement.[35] Among these 40 cases only those of Schlutz seem to present the syndrome he describes, although the cases of Hopkins[14,15] and MacLeod[16] are suggestive.

The following case is presented because it is believed that the syndrome is not as rare as the paucity of reports in the literature would indicate. The child presented here is also of unusual interest because of his favorable progress, which has hitherto not been described as occurring in this syndrome.

CASE REPORT

F. S., a white male child, was first seen on his admission to the Milwaukee Children's Hospital at the age of 16 mos.

He was born at full term and weighed 3.2 kg. Mother had some redness and irritation of the vulva during the latter part of her pregnancy but no subsequent difficulty. He was breast-fed and developed normally until the age of 4 mos. when a red crusted lesion was noted on the lower lip. This gradually spread to involve the entire area about the mouth and nose. Mother's nipples were not involved. Some months later similar lesions appeared on the buttocks and perineum and still later redness and swelling developed about the base of the finger nails. At about the age of 1 yr., he began to show an extensive "infection" of his right foot. Also he seemed to stop growing although his appetite did not seem impaired and he had no diarrhea. Skin cleared temporarily at the age of 14 mos. but weight remained stationary. At the age of 15 mos., the child had an exacerbation of his skin condition associated with teething and a breaking out of "white spots" in his mouth. In addition to the areas previously involved there was now extension to the neck, to areas about all the nails and to localized areas on the extremities. His hair, which had been brown, became lighter. As the skin lesions increased the hair became thinner although the scalp was not involved. Alopecia finally became complete. Except for the skin condition, patient had been well. He had started to walk at 10 mos. of age. He had received an adequate diet. Family history was not contributory. Three siblings, 2 older and 1 younger, were living and well.

Physical examination: There was a complete alopecia. Flat pustular lesions covered with macerated crusts were seen about the mouth and nose, around the neck, about the ears, on the perineum and buttocks with extension to the groin, on anticubital areas, over the olecranon processes, the patellar areas and the malleoli and in areas extending proximally from all the finger and toe nail beds. The

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symmetry of the lesions was striking. All the nails showed paronychial involvement. Mucous membranes of the mouth were clear. Conjunctiva was red and mild photophobia was present. Other physical findings were not remarkable except for the marked dwarfing. He weighed only 7.2 kg. (Fig. 1).

Laboratory examination: Smears from about the mouth, from the nose and from the skin lesions failed to reveal fungi. Cultures from the mouth and stool showed an occasional colony of candida. No further identification of these organisms was done.

Treatment and course: Various forms of local and systemic treatment were given without effect. His condition remained unchanged during the 1st 3½ mos. of hospital stay. Although there were

FIG. 1. F. S., aged 22 mos. Note location and symmetry of lesions, complete alopecia and dwarfing.
FIG. 2. F. S., aged 25 mos. Regrowth of normal brown hair, general good condition, persistence of lesions about mouth and nail beds.

exacerbations and remissions of his skin condition, the skin never cleared completely. No new areas were involved but with each exacerbation there was some increase in size of the areas affected. Crusts about the mouth were always present. The lesions elsewhere began as small papules. These then became vesiculo-pustular in appearance although little or no material could be aspirated from them. When they dried there was some exfoliation of the skin. Then the cycle began anew. The child's general condition remained the same. He gained some weight occasionally only to lose it again. Appetite was only fair but he had no diarrhea. He was alert and obviously intelligent yet he could do little but sit in a chair since his hands and feet were too sore for walking or playing.

The boy was started on thymol orally, 0.192 gm. 3 times daily, 3½ mos. after admission. He had received 8 doses when he developed measles and was transferred to the isolation hospital. During his stay there his skin cleared remarkably. Upon his return to Milwaukee Children's Hospital, it looked the best it had since admission. Three days later, however, the lesions began to appear. Within a week his skin was worse than ever.

Thymol therapy was again begun in the same dosage. Within 6 days the skin lesions were drying and exfoliating to reveal new normal-appearing skin. Thymol was continued for 2 wks. (total dosage 8 gm. [126 gr.]). By July 31, the crusts about the nose and mouth were gone and the entire skin was healing rapidly. The child had become more active and was happily relearning to walk. He was discharged after a total hospital stay of just over 6 mos. He weighed only 7.0 kg. or 0.25 kg. less than on admission. His alopecia was still complete.

During the next 2 mos. the patient was followed in outpatient clinic. He developed some facial

lesions of the papular type and continued to show rather marked redness and thickening of the nail beds. During this time he gained over 2 kg. and a new growth of brown hair appeared on his head. Eyebrows and eyelashes also regrew (Fig. 2).

Patient was readmitted 2 mos. after discharge for a 10 day course of treatment with thymol because of recurrences of lesions about the mouth and perineum. He improved markedly and was not seen again for 4 mos. In this interim he had had an exacerbation attributed by his mother to teething. He was in exacerbation when seen, with lesions about the perineum and thighs as well as about the mouth. The paronychia were still present. He had continued to gain weight, however, and now weighed 10 kg. Most striking was his hair which had changed color completely and was almost white. It was also sparse, coarse and lifeless appearing. For the first and only time in his record a definite membrane resembling thrush was seen in his mouth.

Further laboratory studies were done at this time. Cultures from the mouth, twice repeated, grew C. albicans. Identification was by carbohydrate fermentation tests done both at the Milwaukee Children's Hospital and by the Wisconsin State Laboratory of Hygiene under Dr. Stovall. The organism was pathogenic for a guinea pig. Stool cultures, twice repeated, were negative for C. albicans. Blood agglutinations for C. albicans were positive in 1:10 dilutions at the local laboratory and in 1:20 dilution at the state laboratory. Intradermal skin tests with commercial oidiomycin showed no more reaction after 72 hrs. in the patient than in 10 other children used as controls. However, the sites of the tests on the patient's forearms went on to become typical sites of eruption similar to the other areas of involvement whereas these areas had hitherto not been affected. Similar results were obtained using a vaccine prepared from the autogenous C. albicans.

He was then lost sight of for some time. When seen again he was almost 6 yrs. old. He was reported to have had mild exacerbations and remissions in the interim and several episodes of hair loss and regrowth. He appeared small for his age. Wt. was 16 kg. and ht. 102.5 cm. Actually, these figures indicate more dwarfing than was actually present since all members of the family are small. Patient was exactly the size of the sister 1 yr. his junior. Apparently he had never regained the year's growth he had lost but had otherwise held his own. His hair was white and coarse, typical of its appearance after his relapse in 1941, but he had had sufficient hair to necessitate regular haircuts for the past year. There were no skin lesions except for a slight crusting about the mouth and redness about the nail beds. General condition was surprisingly good.

He was seen again at the age of 8½ yrs. General condition was still excellent. Measurements were not made but he remained the size of his younger sister. Hair was definitely darker than before although not as dark as his normal brown hair. Skin was clear except for a crusted lesion on the right upper eyelid which had been present for some time. Redness of the nailbeds and secondary pitting of the nails were present.

Discussion

This patient presented the typical syndrome associated with C. albicans infection described by Schlutz. Candida were obtained from stool culture and from culture of a thrush-like lesion in the mouth but not from the skin although there was a widespread skin eruption. It would seem that in this case there was a minimum of infection located in the gastrointestinal tract and a maximum of sensitivity to the fungus with an "id" type of skin eruption. This would explain both the difficulty in obtaining fungi from the skin and the rapid response to thymol, an intestinal antiseptic. The mechanism of the effect on growth, especially upon hair growth and pigmentation, remains unexplained although it would seem to be related to some factor in the digestive tract. The prognosis in this case remains grave due to the possibility of systemic involvement but the child's progress so far has been favorable.

Summary

A syndrome associated with candida albicans infection is described. It consists of alopecia, dwarfing, paronychia and eruptions of lesions localized to certain areas of the body. The case of this syndrome presented is unusual in that the child responded to oral thymol therapy and has continued to make good progress.

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SPANISH ABSTRACT

Extraño Síndrome Asociado con Infección Candida Albicans

Un síndrome, asociado con infección Candida Albicans (monilia) y descrito por primera vez por Schultz, incluye un foco de infección en la boca y via gastrointestinal más alopecia, enanismo, paroniquia y erupciones de lesiones de la piel en la cara, perineo y localizadas simetricamente en las extremidades. El caso de este síndroma respondió a la terapia de timol oral (0.192 gm. 3 veces al día) y ha continuado a hacer buenos progresos a pesar de que todavía muestra pruebas de infección Candida Albicans persistentes.

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PHEOCHROMOCYTOMA

Use of N,N-Dibenzyl-B-Chloroethylamine (Dibenamine®) and Piperidino-Methyl-Benzodioxane (Benzodioxane®) in Surgical Therapy

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PHEOCHROMOCYTOMA of the adrenal medulla is being recognized with increasing frequency in cases of arterial hypertension. Its occurrence in children under 13 years of age is infrequent and at the present time only eight patients in this age range have been reported.[1-7]

In the past, emphasis has been placed on intermittent hypertension and increased metabolism as the principal manifestations of these tumors. Green[8] has pointed out, however, that chronic hypertension was present in 37 of the 51 cases which he reviewed.

The active principle secreted by this tumor was recovered first by Beer, King and Prinzmetal.[9] Hyman and Mencher[10] attempted to prove that this principle is epinephrine. Two facts, however, are not consistent with this latter assumption. First, subjects with artificially induced hyperadrenalinemia do not exhibit the proportionate rise in diastolic pressure that is found in patients with pheochromocytoma. Second, the increased cardiac output noted in subjects with induced hyperadrenalinemia is not found in patients with pheochromocytoma. These differences present interesting problems for future investigation.

The differential diagnosis of pheochromocytoma is essentially the differential diagnosis of hypertension in children. Snyder and Vick[1] reviewed this subject and pointed out that one must consider, in addition to pheochromocytoma, the following clinical entities: (1) renal disease; (2) coarctation of the aorta; (3) acrodynia; (4) lead poisoning; (5) Cushing's syndrome; (6) hyperthyroidism; (7) tumors of the hypothalamus; (8) essential hypertension.

Roth and Kvale[11] have advocated the use of histamine to differentiate pheochromocytoma from the other causes of persistent hypertension. Histamine causes a marked increase in blood pressure as well as other manifestations of a paroxysmal attack associated with pheochromocytoma. This test is dangerous and consequently has not been used routinely. Recently, methacholine chloride (mecholyl®, Merck) has been used to precipitate an attack.[12] The use of an agent such as N,N-dibenzyl-B-chloroethylamine (dibenamine®) to counteract the effect of epinephrine would be a more logical and safer method in making a diagnosis. This drug has been used for the first time in establishing the diagnosis of pheochromocytoma in the following case.*

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* Since the writing of this paper, a report on the use of dibenamine® in pheochromocytoma has appeared.[13]

Case Report

J. P., a girl 11 yrs. of age, was admitted to the University of Minnesota Hospitals. Eight days prior to admission, she developed a "flu-like" illness consisting of malaise, fever and anorexia. Four days later a diagnosis of acute pharyngitis and cervical adenitis was made and sulfonamide therapy was instituted. Two days later she complained of pains in the knees and ankles. The next day puffiness of the eyelids was noticed. Urinalysis on this date was reported to show 2 + albumin, 4 + granular casts and 1 + red blood cells. On the morning of admission, she developed headache and vomiting which persisted until the onset of convulsive seizures 3 hrs. prior to admission. She had had scarlet fever 2 yrs. previously and since then had suffered from increased frequency of urination, nocturia and at times incontinence.

Physical examination on admission revealed a thin, well developed, comatose and mildly cyanotic child, perspiring profusely and having repeated convulsions. Seizures were controlled with sodium amytal intravenously. Temperature was 40.1° C., pulse rate 176/min. and blood pressure 174/100 mm.Hg. Pupils were pinpoint size. Under mydriasis the fundi showed marked arteriolar spasm, with artery to vein calibre 1:5. No exudate or hemorrhages were noted. Both optic discs appeared mildly edematous. Tonsils were hypertrophied and mildly inflamed. Coarse rhonchi and crepitant rales were heard over the lung fields. Heart was not enlarged. A harsh, systolic murmur was heard at the 3rd left ICS. No masses were palpable in the abdomen. Normal femoral pulsations were noted. There was generalized hyporeflexia. No edema was present. The presumptive diagnosis at this time was acute glomerulonephritis.

Catheterized urine specimen on admission showed 2 + albumin and occasional casts and RBC. Hemogram Hgb. 15.8 gm./100 cc., WBC 13.6 thousand with leukocytes 84%, lymphocytes 13% and monocytes 3%. ESR was 68 mm. in 60 min. Blood urea nitrogen was 17 mg./100 cc., plasma chlorides, 98 mEq./l. and CO_2 combining power 37.4 mEq./l. ECG showed a tachycardia of 180 beats/min. but was otherwise within normal limits. Portable chest roentgenogram revealed no pulmonary or cardiac abnormalities.

Patient was given magnesium sulfate intramuscularly, as 25% solution, in the dosage of 0.2 cc./kg. body wt. Within 2 hrs. the systolic blood pressure had fallen to 150 mm.Hg. Diastolic pressure was 120 mm. Because of evidence of beginning cardiac decompensation, digitoxin 0.7 mg. was given intravenously. The following day the ECG showed inversion of the T wave in Lead II which was consistent with a digitalis effect. On that day the patient regained consciousness but remained lethargic and somewhat disoriented. Blood pressure continued to be elevated consistently above 150/120 mm.Hg. The dosage of magnesium sulfate was increased, but no response was noted. On the 3rd hospital day, blood pressure rose to 210/150 mm.Hg. 5-allyl-5-(1-methyl butyl) barbiturate (seconal®, Lilly) was added to the magnesium sulfate therapy with only a slight drop in the blood pressure to 180/130 mm.Hg. The following day 250 cc. of 1% magnesium sulfate solution was given intravenously and again only minimal alterations in the blood pressure resulted. The magnesium levels of the blood during and after the infusion did not rise above 2.76 mg./100 cc. Because the levels did not reach those recommended by Winkler,[14] the dosage was increased the next day to 5 gm. in a 2% solution given intravenously. The maximum blood level attained was 3.55 mg./100 cc. (approximately 3 mEq./1.). Little alteration in the blood pressure resulted. That evening it rose to 210/150 mm.Hg. The intravenous administration of 0.13 gm. of theophylline ethylene diamine (aminophylline®) was followed by a transient fall in blood to 128/80 mm.Hg. but it soon rebounded to 230/140 mm.Hg.

Because the diagnosis of acute glomerulonephritis was not conclusive, other causes of hypertension were considered, including pheochromocytoma. The mother was questioned again in more detail regarding the patient's past history. She stated then that the patient had had a bout of headache and vomiting at 2 yrs. of age which was diagnosed as "heat stroke." Since that time attacks of headache, nausea and vomiting had recurred once or twice a yr. Shortly after this conversation, patient had a convulsive seizure involving the entire body. A 0.12 gm. dose of sodium phenobarbital was given intravenously. Blood pressure at this time was 205/155 mm.Hg in the left arm and 250/150 mm.Hg in the left leg. A phlebotomy was performed, removing 200 cc. of blood, with little effect on the blood pressure.

At this point it was decided to try the antiadrenergic substance dibenamine®.* It was given in the

* Obtained through the courtesy of Dr. Mark Nickerson, Department of Pharmacology, University of Utah, and supplied by Givauden-Delawanna, Inc., Delawanna, N.J.

dosage of 6 mg./kg. body wt. intravenously. The response is shown in Figure 1. The period of reduced blood pressure lasted 41 hrs. before stabilizing at 160/110 mm.Hg.

Dibenamine® was given again 3 days later with similar beneficial results. Tetra-ethyl-ammonium chloride was then given intramuscularly in doses varying from 100 to 300 mg. A slight rise in blood pressure resulted from each injection. Examination of the patient on this day revealed increased papilledema, but neurologic findings were normal. Up to this time the clinical course had been characterized by instability of temperature with no obvious infection, excessive perspiration, polydipsia, polyuria, lethargy and loss of memory. Mantoux test and blood and urine cultures were negative. Spinal tap performed on this day showed the spinal fluid pressure to be 150 mm.H_2O; protein 91

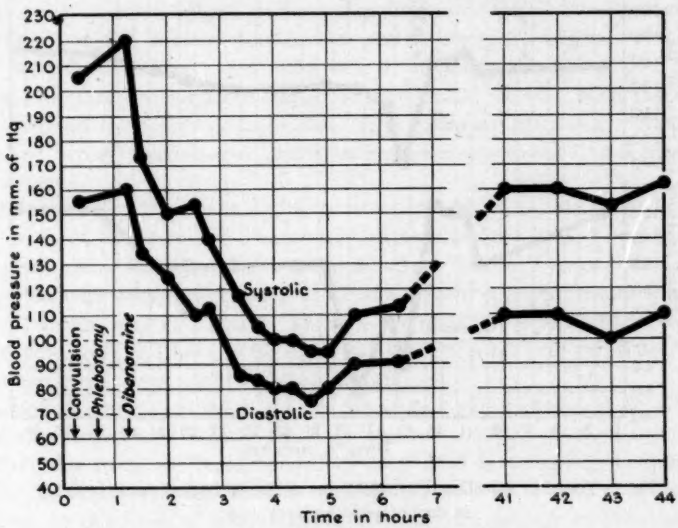

FIG. 1. Prolonged blood-pressure-reducing effect of dibenamine® in case of pheochromocytoma.

mg./100 cc. fluid and no cells were found. Increased protein in the spinal fluid was interpreted as being due to possible vascular accidents occurring during the convulsions. Patient's fluid intake had been restricted to 700 cc./day for the 3 day period. During this period the urine attained a specific gravity of 1.034. Patient was then allowed unlimited quantities of salt-free fluids. Up to 6000 cc. were taken within a 24 hr. period with an output of 4000 cc. of urine having a specific gravity as low as 1.005. Urea clearance was reported to be 68.8% of normal.

Benzodioxane compound,* 933 F., was given 10 days after admission in conjunction with a saline drip as recommended. As shown in Figure 2, a marked drop in blood pressure resulted immediately after the injection. A repeat test the next day had the same effect.

An intravenous pyelogram revealed no tumor masses in the adrenal region but, in view of the response to the antiadrenergic drugs, pheochromocytoma was considered the most likely diagnosis and surgical exploration was undertaken on the 4th day of the period.

Digitoxin was discontinued. Blood pressure was 195/150. Dibenamine® was given preoperatively to prevent an excessive rise in blood pressure that might occur from manipulation of the tumor. Under curare-pentathol anesthesia (abnormally large amounts of the solution being required), a large right rectus incision was made. A mass involving 1/3 of the right suprarenal gland was found. Gentle manipulation of the tumor caused no elevation of blood pressure. Shortly before removal of the tumor, blood pressure was 150/90 mm.Hg. The tumor was easily enucleated. Following its removal, blood pressure fell precipitously to a level too low to measure and the pulse became thready. Epinephrine 1:1000 solution 1 cc. and adrenal cortical extract 10 cc. were given intravenously

* Received from Dr. C. Harrison Snyder, University of Utah.

immediately. Cardiac arrest occurred. Transfusion of blood 2000 cc. and repeated intravenous injections of epinephrine hydrochloride 1:1000 solution in 5 cc. doses were ineffectual. Patient received a total of 50 cc. of epinephrine solution intravenously over a 15 min. period with no effect on pulse or blood pressure. Cardiac massage and injection of epinephrine solution into the myocardium were likewise without effect. Shortly thereafter the patient died.

Autopsy revealed no significant findings other than those resulting from the operative procedure.

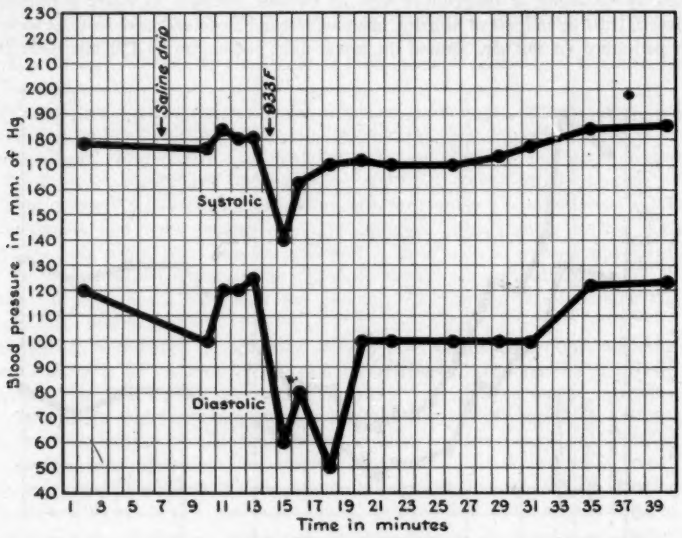

FIG. 2. Transient reduction of arterial hypertension by benzodioxane (933 F.) in case of pheochromocytoma.

PATHOLOGIC REPORT CONCERNING THE EXCISED TUMOR

Gross Examination: The tumor of the adrenal gland weighed 22 gm. and measured 4.5 x 3.5 x 2.5 cm. It was a well circumscribed, encapsulated tumor of fairly soft consistency. The cut surface presented a grayish-brown color.

Microscopic Examination: The section showed a well formed capsule containing at 1 point a few clusters of adrenal cortical cells. The tumor was composed of somewhat polymorphous epithelial tumor cells arranged in rounded clusters and alveoli of rather small size. There were a number of giant forms and scattered mitoses. Uniformly distributed throughout the section were clusters of fine brown pigment. The tumor was moderately vascular.

Conclusion: Pheochromocytoma of the adrenal gland.

DISCUSSION

Acute glomerulonephritis was the first diagnosis considered. Although there were certain abnormal urinary findings, the absence of azotemia in the presence of a sustained hypertension led to the belief that glomerulonephritis was not the primary lesion in this patient. Abnormal urinary findings are not unusual in cases of pheochromocytoma for Green refers to 24 cases with altered renal functions ranging from albuminuria to azotemia. Linneweh's case[2] in a child was treated for chronic nephritis for one year before laparotomy revealed the true nature of the disorder.

N,N-Dibenzyl-B-Chloroethylamine (Dibenamine®):

Nickerson and Goodman[15] were the first to report the effects of dibenamine®, a compound closely related to nitrogen mustard. Their experimental work with cats showed that dibenamine reversed the pressor response to epinephrine and facilitated its depressor effect. Normal animals exhibited little or no response to dibenamine® given slowly over a 10 to 20 minute period. If, however, epinephrine was given after premedication with dibenamine®, a drop in blood pressure resulted. Reflex hypertension and splenic contracture with subsequent liberation of red blood cells and white blood cells caused by anoxia were inhibited. Splanchnic nerve stimulation was not blocked by dibenamine® but the secondary rise in blood pressure that usually occurs was blocked. The other inhibitory sympathetic actions noted were lack of pupillary response to the dark and elimination of epinephrine-induced cardiac arrhythmias. On the other hand, dibenamine® had no effect on epinephrine-induced sinus tachycardia, hyperglycemia, increased pulse pressure and hyperventilation. The results on experimentally induced renal hypertension were equivocal.

Nickerson and Goodman were unable to locate specifically the site or mode of action of dibenamine®. When mixed directly with epinephrine, the pressor response of the latter is enhanced. From their studies they concluded, "The mechanism by which dibenamine prevents the excitatory response of effector cells to epinephrine and sympathin is unknown." It was suggested that the probable site of action is somewhere between the postganglionic fibers and the effector cells. Haimovici,[16] in his frog experiments, agreed with this hypothesis on the site of action of dibenamine®.

Hecht and Anderson[17] extended the dibenamine® studies to man and found the oral administration impractical because the drug was too irritating to the gastric mucosa. The intravenous route was recommended in doses of 4 to 6 mg./kg. body weight in propylene glycol 10% or acid alcohol 50% diluted with 50 to 300 cc. of physiologic saline. Even by this mode of administration, 67% of their subjects exhibited some toxic manifestation, such as local irritation, nausea, psychic disturbance, convulsions, congestion of the nasal mucosa and tingling of the feet.

Trial with dibenamine® in patients with essential hypertension revealed no significant drop in the blood pressure while the patients were in the recumbent position, but orthostatic hypotension occurred regularly. Hypertension induced in man by neosynephrin® and epinephrine was almost completely blocked by dibenamine®. The systolic rise caused by epinephrine was reduced to one half of the control values while the diastolic response dropped on an average of 22.9 mm.Hg. These findings clearly demonstrated the antiadrenergic effects of dibenamine®.

In the case of pheochromocytoma reported here, dibenamine® was the only medication capable of keeping the blood pressure within a relatively safe range for prolonged periods. The first injection caused a drop in pressure from 220/160 mm. to 96/74 mm. Hg. in 3½ hrs. (Fig. 1). Dibenamine® has been used successfully in this case as a means of establishing the diagnosis of pheochromocytoma. This was confirmed by Dr. Hecht.[18]

The response to subsequent injections was not so marked as the first. It seemed that the patient developed a tolerance to repeated injections. Multiple phlebothrombosis at the site of injection, tachycardia and excessive perspiration resulted from the administration of the drug. It was impossible in the present case to evaluate any psychic disturbances,

which have been reported by others as side reaction, since the patient's sensorium was impaired from the beginning of her hospitalization.

Tetra-Ethyl-Ammonium Chloride (Etamon®) and Piperidino-Methyl-Benzodioxane (Benzodioxane®):

The rise in the blood pressure noted after giving etamon® confirms the findings of Moe[19] that this drug has no inhibitory effect on the pressor action of epinephrine. Etamon® acts by blocking the ganglionic transmission of nervous impulses (Acheson and Moe,[20, 21] Lyons et al.[22]).

The results of the benzodioxane drugs as a test for hypertension due to circulatory epinephrine were reviewed in a recent publication by Goldenberg, Snyder and Aranow.[3] Their four patients with pheochromocytoma were given 933 F. in the dosage of 10 mg./sq. m. body surface in a 1 to 2% solution in isotonic saline injected intravenously over a 30 sec. period. A drop of at least 22 mm. systolic and 18 mm. diastolic pressure was obtained in each case which lasted 13 to 16 min. before return to the preinjection level.

No serious untoward side reactions were noted. Only those patients with pheochromocytoma exhibited this vasodepressor response.

The case described in the present report had a similar response to the dosage of benzodioxane recommended by Goldenberg and his coworkers. The blood pressure dropped 144 mm. systolic and 64 mm. diastolic one minute after giving 933 F. The maximum drop was maintained for only one minute, but return to preinjection level did not occur until 22 min. later (Fig. 2).

Surgical Aspects

The two major problems in the surgical handling of a case of pheochromocytoma are the marked elevation of blood pressure associated with the manipulation of the tumor during operation and the precipitous fall in blood pressure following the removal of the tumor.

In the case reported it was desired to prevent any marked increase in blood pressure during operation because the patient tended to develop convulsive seizures when the systolic blood pressure exceeded 200 mm.Hg. For this reason, dibenamine® was given, since it was felt it would be easy to replace epinephrine quickly after the removal of the tumor to counteract the fall in blood pressure. However, as Haimovici[16] showed in frogs, the adrenalytic action of the same dose of dibenamine was equally effective against 1000γ of epinephrine as for 60γ. Apart from convulsive seizure, the danger associated with marked elevations of blood pressure is hemorrhages, particularly in the brain.

There is no unanimity concerning the exact mechanism of the fall in blood pressure and, consequently, there is a variety of opinion as to the best method counteracting it. Bartells and Wall[23] believe that the fall in blood pressure is due to a left ventricular strain secondary to increased peripheral resistance resulting from an excess of circulating epinephrine. They state that the use of epinephrine to counteract this action is unwise and advocate the utilization of digitalis and oxygen during the phase of hypotension. Our patient did receive digitalis prior to operation in amounts sufficient to produce full digitalization, as indicated by the electrocardiogram. When the blood pressure fell, oxygen was given in high concentration, but, in spite of these two measures, the patient died without the hypotension being counteracted.

Burrage and Halsted[24] advocate alternately clamping and releasing the pedicle of the

tumor a number of times until the patient's blood pressure is stabilized. When this occurred, they found it safe to remove the tumor. This is an excellent method of dealing with the problem when a definite pedicle containing a blood vessel is present. In this case, there was no definite pedicle. Nevertheless, it might have been better to clamp off and release a portion of the capsule surrounding the tumor repeatedly until the blood pressure had become stabilized. There can be no question that the best way of handling the surgical removal of this tumor is to permit stabilization of the blood pressure before the tumor is removed entirely.

MacKeith[25] has advocated the following preoperative and postoperative measures: 1. Avoidance of anesthetic agents that profoundly influence the blood pressure. 2. Use of the abdominal approach for localizing the tumor followed by re-exploration through the lumbar route. 3. Epinephrine in 1:100,000 dilution ready to be given intravenously. 4. Transfusion with whole blood if the blood pressure fails to respond to epinephrine. 5. Administration of adrenal cortical extract after removal of the tumor.

These points are in essential agreement with those advised by Thorn.[26] We agree also with the recommendations of MacKeith, but we believe that the operation can be done entirely through the abdominal approach. It is obvious from the protocol that large amounts of epinephrine, as well as whole blood, were given to this patient without benefit. Other authors[10,27,28] suggest use of adrenal cortical extract postoperatively and Hyman and Mencher[10] give sodium chloride and suprarenal extract before and after surgery so that, in the event of atrophy or absence of the other adrenal, the patient will receive substitution therapy. In this case it seems unlikely that the fall of blood pressure was due to the absence or diminution of suprarenal extract because the left adrenal gland was apparently normal and only ⅓ of the right adrenal gland was removed with the tumor.

The mortality rate following surgery of this condition in childhood is extremely high. Of the seven cases operated upon, four (58%) died.

The use of whole blood, suprarenal extract, oxygen and digitalis as carried out in this patient does not always prevent the hypotension following the removal of the tumor. It leads one to believe that perhaps there is more involved than merely the removal of epinephrine from the circulating blood stream.

Summary

A case of pheochromocytoma in a girl 11 years of age is reported. The difficulties in establishing the diagnosis as well as the other pathologic states which must be considered in the differential diagnosis of this condition are discussed.

A new preparation, N,N-dibenzyl-B-chloroethylamine dibenamine®, was used in establishing the diagnosis and in the therapy of the case. The drug was found useful in reducing the hypertension but its preoperative use was apparently ill-advised.

The case study confirms the findings of others that benzodioxane compounds are helpful diagnostic aids and that tetra-ethyl-ammonium chloride has little value in either the establishment of the diagnosis in or treatment of patients with pheochromocytoma.

The problems associated with surgical care of patients with pheochromocytoma are discussed.

Acknowledgment

The authors wish to thank Dr. Irvine McQuarrie for his encouragement during the course of this study.

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SPANISH ABSTRACT

Feocromocitoma

Se presenta un caso de feocromocitoma. Se acentuan las dificultades en establecer la diagnosis. Se deben considerer las siguientes condiciones en un diagnóstico diferencial: (1) enfermedad renal; (2) coarctación de la aorta; (3) Acrodinia; (4) plumbismo; (5) síntomas de Cushing; (6) hipertiroidismo; (7) tumores del hipotalamus; (8) hipertensión esencial.

Se usó la Dibenamine (N,N-dibencilo-B-cloroetilamina) en el diagnóstico y en el tratamiento. La Dibenamina fué útil en controlar la hipertensión; pero su uso preo-operativo no lo fué.

Los compuestos de Benzodioxane son ayudas diagnósticas utiles; el cloruro de amonio tetraetilo es de poco valor en el establecimiento del diagnóstico o en el tratamiento.

El paciente recibió después de la operación digitalis, extracto cortical suprarenal y solución salina. Durante la cirugía e inmediatamente después de remover el tumor, ella recibió epinefrina y transfusiones de sangre. No se pudo combatir la hipotensión y murió.

El mejor procedimiento quirúrgico es la disección cuidadosa con sujeción gradual del pediculo del tumor para poder alcanzar la estabilización de la presión arterial antes de la extirpación del tumor.

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BASAL METABOLIC RATE IN OBESE CHILDREN

With a Note on the Basal Metabolic Rate in Dwarfs

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IT HAS been well established that obesity in adults is due primarily to an excessive intake of food and not to a disorder of heat production. Evidence for this view has been recently summarized by Newburgh and Conn.[1] The systematic studies of Bruch[2-7] indicate that in children as well obesity is usually caused not by an endocrine or metabolic disorder but rather by a functional disturbance of appetite regulation, usually of psychic origin.

Although it is generally accepted that the basal metabolic rate is normal in adults with obesity,[8-11] no such uniformity of opinion exists in the pediatric literature. On the contrary, observers[12-14] with considerable experience in pediatric endocrine problems have tended to agree with Bruch[3] in the following statement: "The figures observed and the correlations calculated lead to the conclusion that determinations of basal metabolism as ordinarily carried out and as conventionally reported are an untrustworthy guide when the clinician is seeking to estimate the part played by the thyroid in the pathogenesis of obesity. Calculation of the basal metabolic rate according to different standards furnishes widely diverging results, none of which can be considered the correct one. The basal metabolism of obese children should remain the object of clinical research until the many known components which enter into its computation are better recognized and understood."

It is the purpose of this paper to present the results of 524 observations of the basal metabolism of 348 obese children. Analyses of these results indicate that the confusion mentioned arises from errors in the choice of methods of calculation of the basal metabolic rate. Furthermore, if our concept of "correctness" be conformity of the results with the clinical observations that there is no metabolic disorder in obese children, then use of the Child Research Council surface area-age standards[15] yields acceptable findings.

SOURCE OF DATA

The children studied ranged in age from 6 to 15 years and consisted of two groups. Three hundred ninety-five observations were made on 301 children who had been referred to the pediatric endocrine clinic of the New York Hospital because of obesity. Their weights ranged from 20 to 150% above the mean weights for age of the normal children in the Child Research Council study.[15] The remaining 129 observations were made on 47 children who are members of the Child Research Council group and who

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in the course of their development have come to be from 10 to 35% above the mean weights for age. The observations at the New York Hospital were made by trained technicians using a Benedict-Roth apparatus in the routine basal metabolism laboratory of the hospital. These children had no special instructions or treatment but received customary tactful reassurance to help allay apprehension. The Child Research Council children had had repeated determinations of the basal metabolism but this has been shown to be without effect on the results obtained for these children.[16] All Child Research Council determinations were made with a closed chamber.[17]

Choice of a Standard for Reference

It is generally accepted that age, height and weight will independently affect the rate of basal oxygen consumption.[18] For example, individuals of the same height

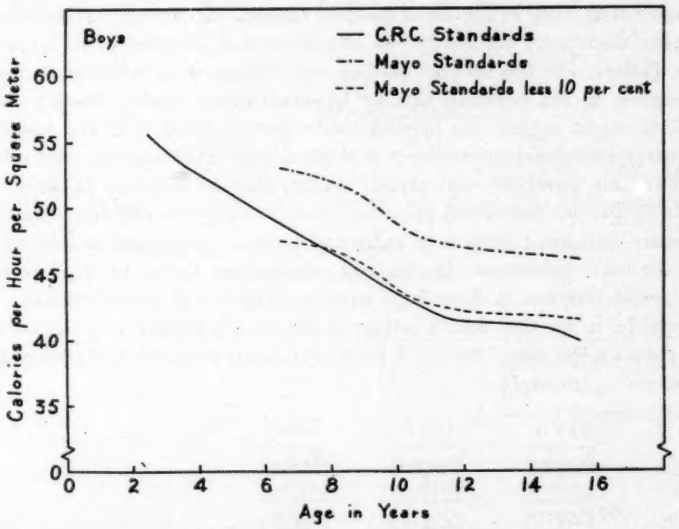

Fig. 1. Comparison of Child Research Council and Mayo standards for cal./hr./sq. m. referred to age for basal metabolism of boys.

and age but of different weights will have widely different oxygen consumption. Individuals of the same weight and age but of different heights will also use oxygen at different rates, but the effect of the differences in height is not as striking as that of differences in weight. Finally, individuals of different ages will have different rates of oxygen consumption when weight and height are kept constant. The most satisfactory standard of reference for adults, i.e., one which permits comparison of individuals of widely different sizes or configuration, is one based on age and surface area. This ordinarily is calculated from height and weight.[18] Whether the satisfactory use of a surface area standard stems from valid physiologic reasons[18] or is fortuitous and dependent on the accidental use of a physical standard of reference which approximates the ¾ power of the weight[19] does not affect the considerations of this paper.

Whence comes the confusion? Inspection of Figure 1 prepared from the data of Lewis,

TABLE I

EXAMPLE OF EFFECT OF CHOICE OF STANDARD ON CALCULATED DEVIATION OF BASAL METABOLIC RATE

Patient 118	Male	Age: 10 yrs.
Wt.: 59.5 kg.	Ht.: 148 cm.	Surface area: 1.52 sq. m.
Cal./hr. found:		56.1
Cal./hr./sq. m. found:		36.9

	C.R.C.	Mayo
Standard cal./hr./sq. m.	42.8	47.7
Percentage deviation (B.M.R.)	−14	−23

Duval and Iliff[15] yields an answer. It is seen that the Mayo standards[20] are approximately 10% higher than those of the Child Research Council. No obvious explanation is available for this discrepancy but its effect on interpretation is presented in the simple example cited in Table I. For this 10 year old boy, the findings of a deviation of minus 14% would suggest to the physician that no hypometabolism existed, whereas a report of minus 23% might suggest that hypothyroidism was contributing to the discrepancy between energy intake and output. Since it is not simple to decrease the food intake of an obese child, any possibility that thyroid therapy may be indicated is usually received favorably by patient, parent and physician. Unfortunately, the administration of thyroid in customary therapeutic doses to an individual without hypothyroidism leads to no elevation of the basal metabolism. In the cited example, the failure of response to thyroid therapy would lead one to discard the tentative diagnosis of hypothyroidism. The next step would be to say that determinations of the basal metabolic rate are untrustworthy guides. Actually, the use of the Child Research Council standards will prevent this situation from arising frequently.

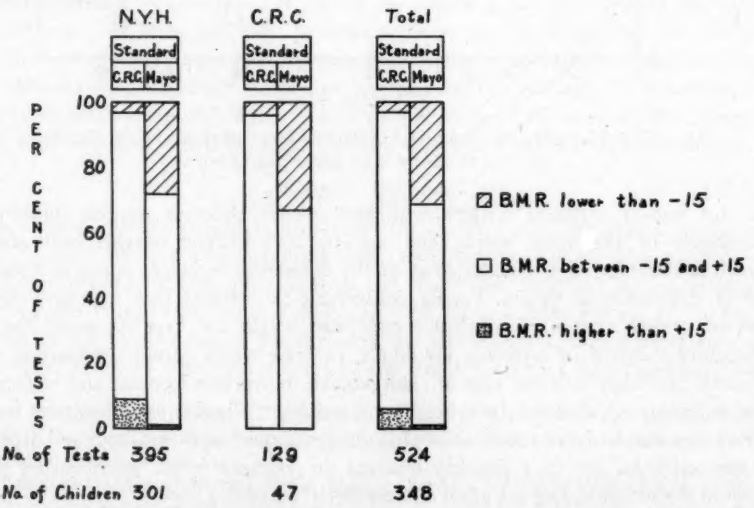

FIG. 2. Comparison of basal metabolism of 2 groups of obese children as calculated by Child Research Council and Mayo standards for cal./hr./sq. m. referred to age.

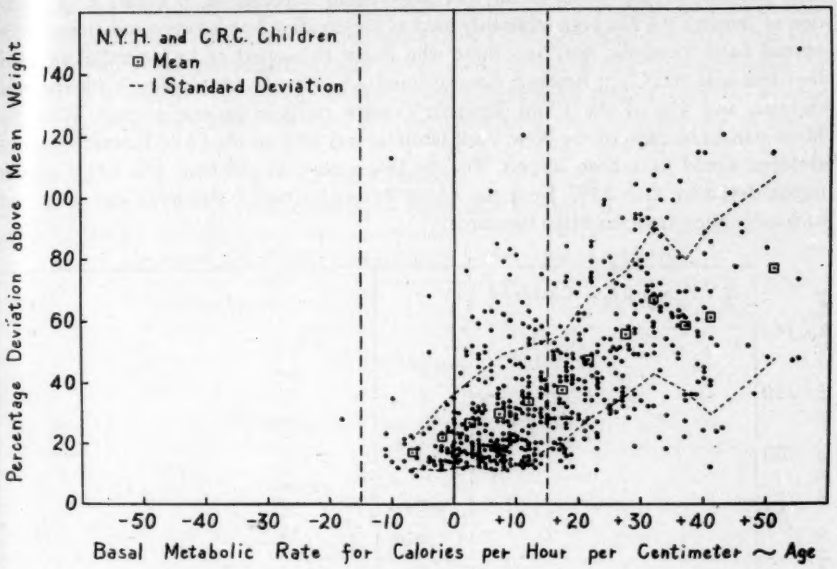

FIG. 3. Effect of degree of obesity on deviation of basal metabolic rate when ht.-age standard is used.

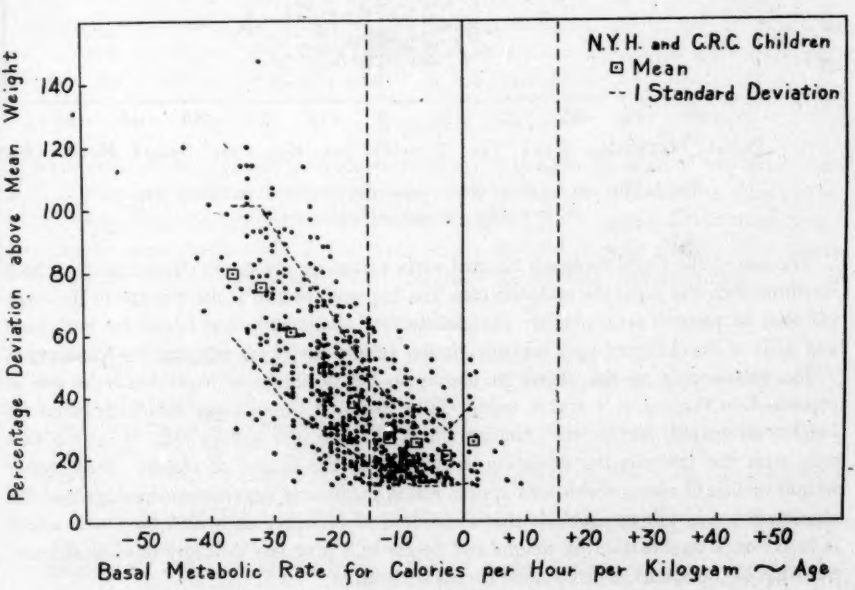

FIG. 4. Effect of degree of obesity on deviation of basal metabolic rate when wt.-age standard is used.

A summary of the results of the 524 observations is presented in Figure 2. A deviation of minus 15% has been arbitrarily used as the dividing line between individuals with normal basal metabolic rates and those who might be suspect of hypometabolism. It is seen that with the Child Research Council standards only 3% of the New York Hospital children and 4% of the Child Research Council children became suspect. With the Mayo standards, 28% of the New York Hospital and 33% of the Child Research Council children would have been suspect. For the two groups of children, 3% had a greater minus deviation than 15% from the Child Research Council standards and 29% had such a deviation from the Mayo standards.

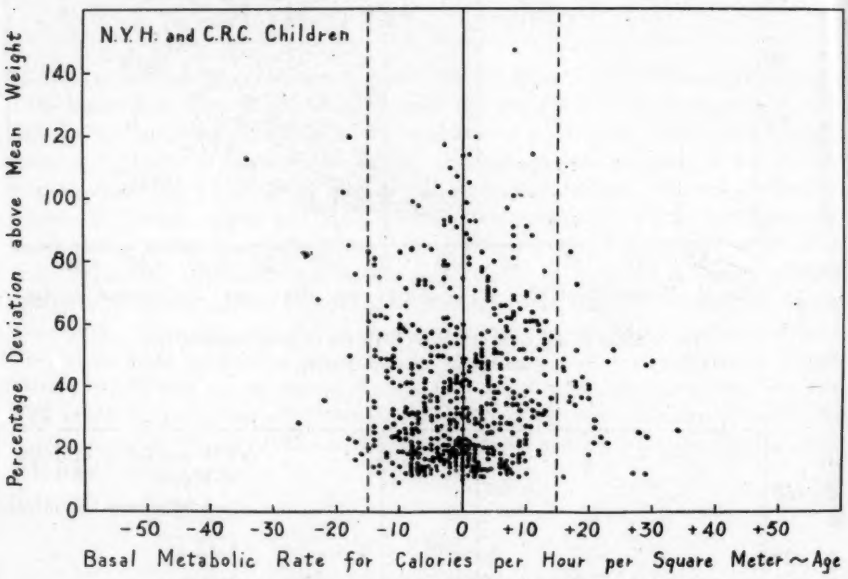

FIG. 5. Effect of degree of obesity on deviation of basal metabolic rate when surface area-age standard is used.

The use of the Child Research Council surface area-age standards yielded results which conform with the generally accepted idea that hypometabolism is not present in the large majority of patients with obesity. This satisfactory relationship was found for both boys and girls at the different ages studied. Similar results have been reported by Mossberg.[21]

The relationship of the degree of obesity to the deviation in basal metabolic rate is expressed in Figures 3, 4 and 5, using Child Research Council age standards based on height, on weight, and on the combination of the two into surface area. It is seen that only with the latter is the deviation unaffected by the degree of obesity. With either weight or height alone, distortions appear whose magnitude depends on the degree of the obesity. It seems fair to conclude that a standard of reference such as surface area which is based on a combination of weight and height will give less difficulty in clinical interpretation of the results as determined for obese children.

At the risk of confusing the issue, we would like to add one point about the interpre-

tation of the basal metabolic rate in dwarfs. In Table II are presented the rates of four proved hypothyroid dwarfs for comparison with six nonhypothyroid dwarfs. It is seen that only two of the nine determinations on the nonhypothyroid dwarfs showed metabolic rates of less than plus 10%. The remaining six ranged from plus 16 to 44%. For the proved hypothyroid dwarfs, all were less than plus 10%, but only one was as low as

TABLE II

BASAL METABOLIC RATES OF 10 DWARFS

Deviation from Child Research Council Surface Area—Age Standard			
Nonhypothyroid		Hypothyroid	
A.K.	+ 3	H.T.	− 4
J.B.	+16		+ 6
	+27	G.C.	−16
	+44	D.C.	− 4
	+ 7	P.H.	+ 1
P.McA.	+17		± 0
M.McE.	+30		
E.M.	+27		
P.N.	+31		
Total determinations:	9	6	
Number below +10%:	2	6	

minus 16%. Use of a weight or height standard did not help clarify the interpretation. Actually it would seem that when one finds a basal metabolic rate in a dwarf which is not elevated above plus 10%, when referred to Child Research Council surface area-age standard, one should suspect the possibility of hypothyroidism.

SUMMARY

An analysis of the results of 524 observations of the basal metabolism of 348 obese children is presented. Since only 3% of the basal metabolic rates were lower than minus 15% of the Child Research Council surface area-age standards, it is suggested that these standards can be used satisfactorily in the management of children with obesity. For reasons which are not obvious these standards do not suffice for children with dwarfism.

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SPANISH ABSTRACT

Proporcion Metabolica Basal en Niños Obesos con Una Nota en la Proporcion Metabolica Basal en Enanos

Se presenta un análisis de los resultados de 524 observaciones del metabolismo basal de 348 niños obesos. Como solamente el 3% de las proporciones metabólicas basales fueron más bajas que menos 15% de las normas de edad y area de superficie del Consejo de Investigación del Niño (Child Research Council), se sugiere que se usen estas normas satisfactoriamente en el manejo de niños con obesidad. Por razones que no son obvias, estas normas no bastan por niños con enanismo.

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DOUBLE AORTIC ARCH

Report of Two Cases and Review of the Literature

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A DOUBLE aortic arch is the result of the persistence of both fourth branchial arterial arches; the arches fuse with the dorsal aortae to form the descending aorta. The resulting anomaly constitutes a vascular ring. Most commonly a large right aortic arch passes to the right of the esophagus and trachea in a posterior direction, then turns to the left, passing behind the esophagus and trachea, and connects with a small left aortic arch. The small left aortic arch passes laterally to the left in front of the trachea and then turns posteriorly to join the right aortic arch which continues downward as the left descending aorta. Usually, the right common carotid artery and then the right subclavian artery arise independently from the right aortic arch, and the left common carotid artery and the left subclavian artery arise from the left aortic arch.

Hommel[1] in 1737 published the first description of a double aortic arch. Since then over 40 cases of proved double aortic arch have been described. Blincoe, Lowance and Venable[2] have reviewed the anatomic variations which may occur in the anatomy of a double aortic arch.

Wolman[3] emphasized the clinical picture of stridor and dysphagia which may occur during the first few months of life. He felt that constriction of the esophagus and trachea by the double aortic arch produces an easily recognizable syndrome. His criteria for the diagnosis of a double aortic arch included susceptibility to bronchopneumonia, stridulous breathing, chronic cough, head retraction, malnutrition and increased respiratory distress during feeding.

Arkin[4, 5] was the first to describe the roentgenographic findings in patients with double aortic arch and to correlate these with the clinical signs. According to him, the clinical signs of double aortic arch are: dullness to the right of the sternum, visible systolic pulsation in the right supraclavicular fossa, displacement of the trachea to the left, tracheal tug, obstruction to the free passage of a stomach tube at the level of the third dorsal vertebra with pulsation transmitted along the tube, and maximum intensity of the aortic second sound in the region of the head of the right clavicle. His roentgen criteria include the following points: In the antero-posterior position, the shadow of the aortic knob lies to the right and displaces the esophagus and trachea to the left. In the right anterior oblique position, the aorta lies behind the trachea and esophagus and displaces them anteriorly. In some instances, where both arches are patent, a smaller second shadow representing the anterior arch may be visible in front of the trachea. In the left anterior oblique view, there is a wide shadow of the ascending aorta and confirmatory evidence of anterior displacement of the esophagus and trachea.

Recently Gross,[6] Gross and Ware[7] and Sweet et al.[8] have reported a total of four cases in which division of a double aortic arch was undertaken successfully for the relief

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of symptoms of constriction. A fifth case has been recorded by Steinberg[9] and referred to by Gibson.[10] Inasmuch as surgery now offers apparently permanent relief from such symptoms, clinical diagnosis of the condition has become of added importance. The purpose of this report is to present two cases of double aortic arch and to review the literature.

Case Reports

Case 1. D. L., a white male infant 5 wks. of age, was admitted to the Harriet Lane Home with the complaints of difficult, loud, labored, wheezing breathing and a brassy cough.

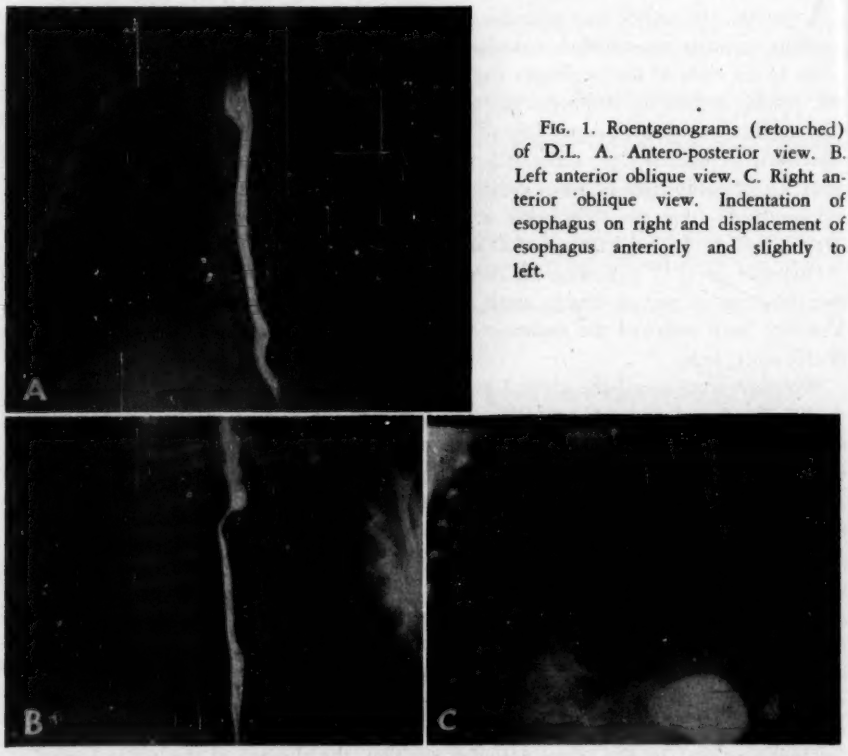

Fig. 1. Roentgenograms (retouched) of D.L. A. Antero-posterior view. B. Left anterior oblique view. C. Right anterior oblique view. Indentation of esophagus on right and displacement of esophagus anteriorly and slightly to left.

Family history was noncontributory apart from asthma on the maternal side. He had been a full term infant and weighed 2.5 kg. at birth. His mother thought that his respirations were noisy during the first few days of life. There was no feeding difficulty. Between the 3rd and 4th wks. of life, he developed a watery nasal discharge and his respirations became rapid, noisy and wheezing. Each feeding was prolonged because of the respiratory distress. There was, however, no dysphagia, regurgitation or vomiting. At about 4 wks. of age, he developed a brassy cough which was worse at night. He was referred to the Harriet Lane Home with the tentative diagnosis of vascular ring.

Physical examination: Temperature 37.2° C. (rectal); pulse 120/min.; respirations 40/min.; wt. 3.7 kg. General appearance was that of a well developed, well nourished white male infant who did not appear in acute distress. There was no cyanosis. He had an inspiratory whistle and at times a croupy, brassy, expiratory stridor. Chest was symmetric and moved normally with respiration. Coarse rhonchi were audible throughout the lungs. Heart was not enlarged and no murmurs were audible. Blood pressure could not be obtained in either arm. Femoral artery pulsations were rather weak. Systolic blood pressure in the leg was between 80 and 85 mm. of mercury.

Fluoroscopy revealed that the heart was not enlarged and the lungs were clear. Aortic knob was situated on the right. Esophagram showed that the esophagus deviated to the left at the level of the aortic arch. In the right anterior oblique position the esophagus was displaced anteriorly by the aorta at the same level. This anterior displacement of the esophagus was confirmed when the patient was turned into the left anterior oblique position. Roentgenogram substantiated this impression (Fig. 1).

These findings indicated that the aorta arched to the right and passed behind the esophagus and trachea to descend on the left. No esophageal obstruction was demonstrated by the passage of a #10 F catheter into the stomach and no acute cardio-respiratory distress or unusual symptoms were produced by this procedure. It was concluded that the symptoms did not justify surgical intervention

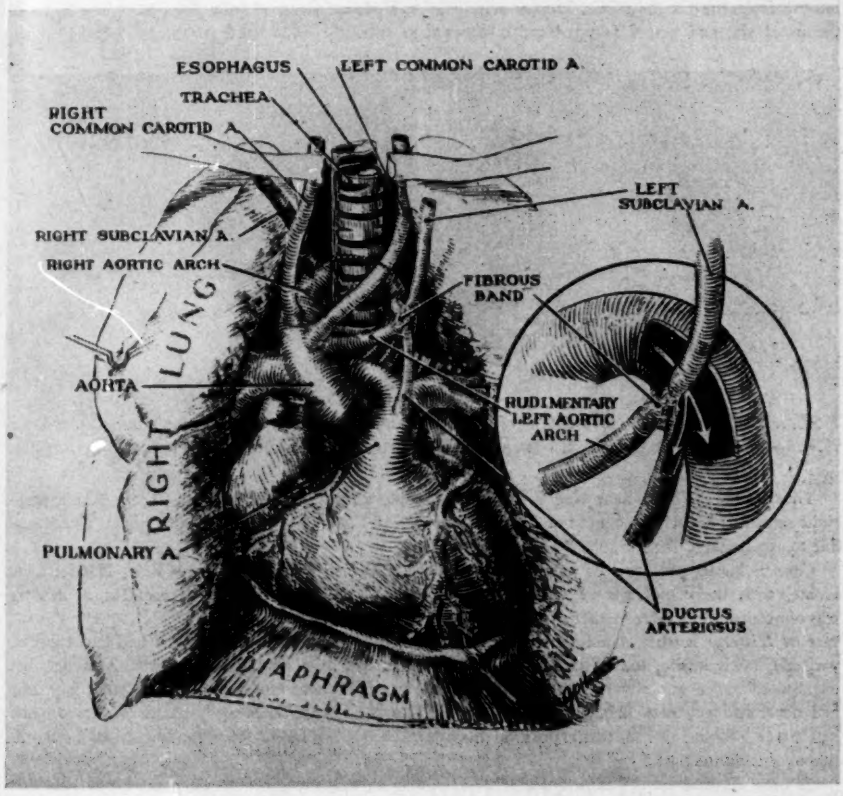

FIG. 2. D.L. Anatomic arrangement of great vessels and their branches, showing double aortic arch with large right aortic arch and small partially obliterated left arch with left descending aorta. Inset: Enlargement showing origin of left subclavian artery from fibrotic portion of left arch.

and the infant was discharged to be followed in the cardiac clinic. The day after discharge he was brought back to the dispensary dead. He had developed sudden respiratory distress while being fed in the dark when lying on his back. It seemed clear that he had died from aspiration of his formula.

Autopsy (Dr. D. J. Birmingham): Chief interest centered about the heart and lungs. Tracheobronchial tree was filled with frothy blood-tinged mucoid material, part of which was identified as formula. Lungs were edematous and microscopic sections showed that there was acute pulmonary congestion with areas of early lobular pneumonia.

Heart was essentially normal. No valvular deformities were present. Foramen ovale was covered by a valve-like flap which admitted a probe along the inferior border. Ventricular septum was intact.

Aorta arose normally from the left ventricle and divided into a large right aortic arch and a small left aortic arch (Fig. 2). The right component passed upward and backward to the right of the trachea and esophagus, turned to the left to pass behind these structures, and descended just to the left of the midline. Right aortic arch gave off the left common carotid artery, then the right common carotid artery and finally the right subclavian artery. A rudimentary left aortic arch arose from the left lateral wall of the ascending aorta just below the origin of the left common carotid artery and passed laterally in front of the trachea. It was attached to the descending aorta by a fibrous strand of tissue at the level of the aortic end of the ductus arteriosus as shown in Fig. 2. At this point, the lumen of the left aortic arch was completely obstructed. Left subclavian artery originated blindly from the fibrous tissue. Ductus arteriosus was patent. It arose from the descending aorta at the usual site and passed forward and downward to enter the main trunk of the pulmonary artery.

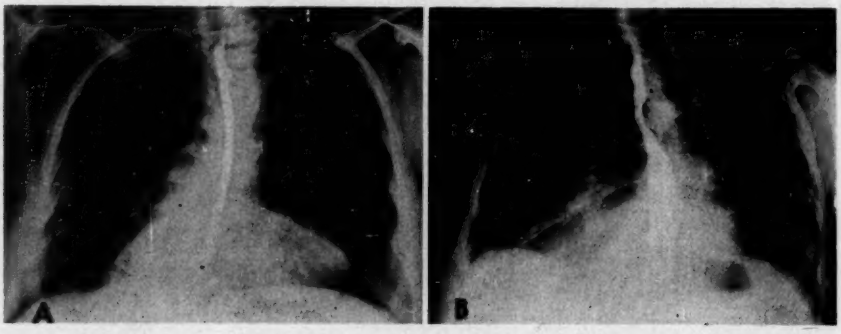

FIG. 3. Roentgenograms (retouched) of N.P. A. Antero-posterior view. B. Left anterior oblique view. Indentation of esophagus on left and displacement of esophagus anteriorly and slightly to right.

Thus there was a vascular ring formed by a double aortic arch which was comprised of a large right retro-esophageal component and a small partially obliterated left anterior component. Death was due to aspiration of the formula.

Case 2, N. P., a 20 yr. old white French girl, was first seen in the Cardiac Clinic, Harriet Lane Home, with the complaints of cyanosis since birth and limited exercise tolerance. Family history was noncontributory. Her mother's health during pregnancy was excellent.

Past History: Birth was normal at full term. Her development was normal. She had had rubeola, varicella, otitis media, tonsillitis and appendicitis. She had been cyanotic since birth. Although her exercise tolerance was always limited, she was able to walk about one half mile at a slow gait. She had never had any hemoptysis, melena, convulsions, loss of consciousness, dysphagia or stridor. She had never adopted the squatting position for relief of her symptoms. Her condition had been stationary during the past 2 yrs.

Physical Examination: Temperature 37.2° C.; pulse 85/min.; respirations 20/min.; blood pressure, right arm 120/100 mm. Hg., left arm 100/70 mm. Hg. She was a cyanotic, cooperative, intelligent girl. There was extreme clubbing of the fingers and toes. Chest and back were deformed by kyphoscoliosis of a severe degree.

Heart was not enlarged. No thrill was palpable. There was a harsh grade 3 systolic murmur over the whole precordium, maximal in the 4th left interspace. Lungs were clear to percussion and auscultation. Liver and spleen were not palpable.

Arterial blood analysis revealed the following: oxygen content 19.1 vols. per cent; oxygen capacity 31.2 vols. per cent; oxygen saturation 61/100 ml.; carbon dioxide content 25.6 vols. per cent. RBC 8.1 million/cmm.; Hgb. 22.4 gm./100 cc.; hematocrit reading was 68.

ECG showed a right axis deviation in the standard limb leads and right ventricular hypertrophy in the unipolar precordial leads.

Fluoroscopic findings were difficult to interpret owing to the marked scoliosis. Lungs were clear and quiet. Heart was normal in size. There was a concavity of the upper portion of the left border of the cardiac shadow. Apex was prominent. Esophagram showed indentation of the esophagus on the left in the region of the aortic knob which appeared to be in its normal position. In the left anterior oblique position, the esophagus was angulated sharply anteriorly just below the aortic knob, suggesting the presence of a large retro-esophageal vessel. Chest roentgenograms confirmed these observations (Fig. 3). These findings, which were similar to those described by Paul[11] were interpreted as demonstrating an aorta which arched to the left in the normal manner and then passed behind the esophagus to descend on the right.

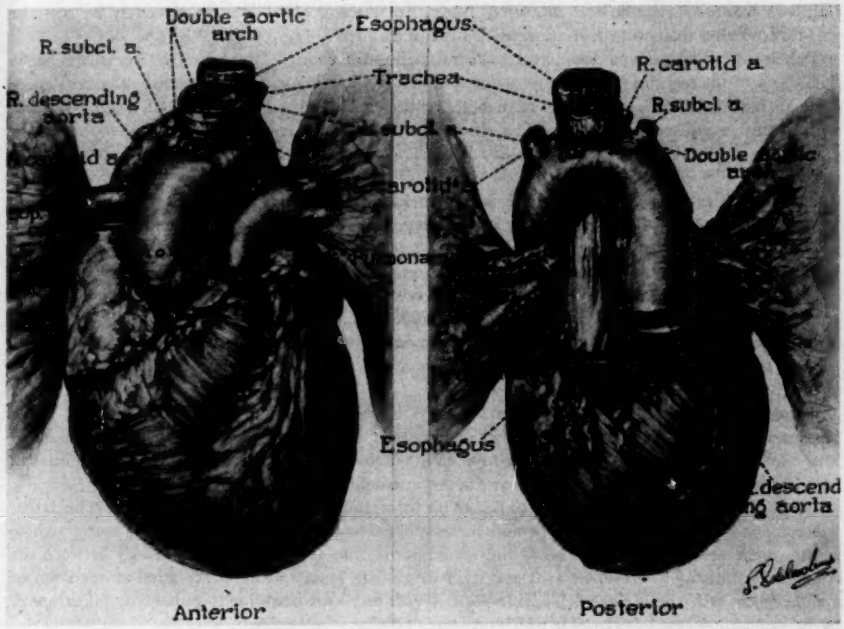

FIG. 4. N.P. Autopsy findings showing double aortic arch with large left aortic arch, small right aortic arch and right descending aorta.

Clinical diagnosis was tetralogy of Fallot with a left aortic arch and a right descending aorta. It was felt that the retro-esophageal aorta was not a contraindication to surgery. Therefore, the patient was recommended for a Blalock-Taussig operation.

Operation was performed by Dr. Alfred Blalock 10 days after admission. Incision was made on the right. Aortic arch was unexpectedly found on the right side. Right subclavian artery arose directly from the arch of the aorta. An anastomosis was made between the proximal end of the subclavian artery and the side of the right pulmonary artery. At the end of the operation a continuous thrill could not be felt in the pulmonary artery, but it was thought that blood was flowing through the anastomosis during systole.

Patient failed to show any immediate improvement. There was no diminution of cyanosis and a continuous murmur was not audible. Bloody fluid was aspirated from the right chest cavity on the 2nd, 5th, and 6th postoperative days. She developed a superficial thrombophlebitis of the right leg at the site of the intravenous infusion. During this period she had an intermittent fever which had subsided by the 13th day. Mobilization was begun the next day. On the following day she complained of severe pain "in the heart," rapidly became deeply cyanotic, and lapsed into coma. In spite of

the administration of oxygen, coramine and atropine, she became progressively more cyanotic, and died 20 min. later.

Autopsy (Dr. A. R. Nelson): The pertinent findings were limited to the heart, great vessels and lungs. Heart appeared enlarged. Right auricle was markedly dilated. Tricuspid valve was scarred and thickened and verrucous nodules were visible along the line of closure; microscopic sections, however, showed no evidence of inflammation of the valve.

Right ventricle was hypertrophied and dilated; it measured 17 mm. in thickness. There was a high ventricular septal defect which measured 2.0 cm. in diameter. Infundibulum of the right ventricle was small. Pulmonary valve was bicuspid. Margins of the cusps were fused so that there was only a tiny lumen at the apex of the valve. This lumen measured 2 mm. in diameter. Pulmonary ring was markedly stenotic and measured 1.8 cm. in circumference. Pulmonary artery beyond the valve was smaller than normal. It measured 1.3 cm. in diameter.

Pulmonary veins entered the left auricle normally. Left auricle was normal. There was some thickening of the margins of the cusps of the mitral valve. Left ventricle was hypertrophied and measured 15 mm. in thickness. Sections from both ventricles showed numerous foci of hyaline scarring with extensive replacement fibrosis. The absence of any cellular reaction suggested that these were embolic in origin. A recent antemortem thrombus, 1.5 cm. in diameter, lay free in the left ventricular cavity.

Aorta was dextroposed. It arose from both ventricles and overrode the ventricular septum. There was a double aortic arch (Fig. 4). The larger component, which measured 13 mm. in diameter, lay on the left and turned to the right behind the trachea and esophagus to join the smaller right aortic arch which measured 8 mm. in diameter. Aorta descended to the right of the esophagus. Left common carotid artery and the left subclavian artery originated separately from the left arch. Ductus arteriosus, which arose from the left arch, was obliterated. Smaller right aortic arch gave off the right common carotid artery and the right subclavian artery. There was slight constriction of the trachea and esophagus. Anastomosis between the end of the right subclavian artery and the side of the right pulmonary artery was patent.

Lungs were collapsed and there were 2 infarcts in the left lung. One infarct in the left upper lobe measured 3 cm. in its greatest diameter. The other infarct involved the lower half of the left lower lobe. No gross emboli were found, but in 1 microscopic section a portion of an embolus was seen impacted in a small pulmonary artery. There was an old infarct in the spleen.

Thus this patient had a tetralogy of Fallot in association with a double aortic arch. The larger left component of the arch passed behind the esophagus and joined the smaller right aortic arch to form a right descending aorta. The finding of an aortic ring explained the discrepancy between the clinical diagnosis of a left aortic arch and right descending aorta and the observation at operation of a right aortic arch and a right descending aorta. Death may have been due to pulmonary infarction or to the thrombus in the left ventricle which may have acted as a ball valve.

Discussion

The two cases illustrate two of the variations which may occur in the anatomy of a double aortic arch. The first had a large right arch with a retro-esophageal component and a left descending aorta, the second a large left arch with a retro-esophageal component and a right descending aorta. They further illustrate that a double aortic arch on the one hand may give rise to symptoms of constriction and on the other hand may be asymptomatic.

A review of the literature reveals considerable confusion as to the distinction between a double aortic arch, a persistent right aortic arch with a retro-esophageal aorta, and a simple right aortic arch. From the practical standpoint, the distinction of cases of double aortic arch from other causes of vascular ring is not important as the treatment of all types of vascular ring is the same. Clinically, however, it is important to distinguish cases of double aortic arch and other malformations accompanied by a retro-esophageal vessel from cases of simple right aortic arch with a right descending aorta. In the former

instance, the condition may be amenable to surgery, whereas in the latter, there is no necessity for surgery. In many reports such a differentiation has not been made. For example, Blackford et al.[12] in 1932 included cases of double aortic arch in their consideration of cases of persistent right aortic arch "because they cannot be distinguished clinically." Again, Sprague et al.[13] reported two patients, alive at the time of the report, who suffered from dysphagia, as examples of persistent right aortic arch but advanced the view that probably a vascular ring was present in each case.

It is obvious that certain criteria must be laid down before a clear picture can be obtained. Cases which are reviewed in this paper have been limited to those which have been proved at autopsy or operation to have a double aortic arch with or without obliteration of part of the left arch. Some authorities may consider cases of double aortic arch with partial obliteration of the left arch as a separate entity, but, nevertheless, a complete ring is present and embryologically this ring is made up of the two components of a double aortic arch. Furthermore, the symptoms and the treatment are the same as in cases of double aortic arch where both arches are patent. Therefore, such cases are included in this series.

In addition to the two cases reported in this paper, 47 other cases of double aortic arch have been reported in the literature. Table I lists 19 cases of patients under 2 years of age who died or had successful operation; Table II is comprised of 23 patients over the age of 2 years. In Table III is a group of seven cases which are included as a supplement to those in Tables I and II, but the original reports were not available. Although their exact ages are not known, most of the patients in Table III were stated to be adults. These cases have been included in the following analysis wherever relevant data have been stated in the references which quote the original reports.

Analysis of these cases reveals a striking correlation between the occurrence of severe symptoms and the duration of life. As is shown in Table I, all but two of the infants (Cases 18 and 19) suffered from symptoms referable to the double aortic arch. In Case 18 there was a nonfunctioning left ventricle with a ventricular septal defect and the patient died in coma following convulsions; in Case 19 the patient died from bacillary dysentery, peritonitis and bronchopneumonia. All the other infants suffered from symptoms and all died as a direct result of the malformation with the exception of three on whom successful operations were performed. It is worthy of note that the infant reported by von Siebold[14] (Case 1), in whom there was a transposition of the great vessels, suffered from symptoms related to the constriction of the trachea by the vascular ring and died from exhaustion.

Five infants underwent surgery; three of these survived and two died. Two were reported by Gross[6] (Case 7) and Gross and Ware[7] (Case 12) on whom successful operations were performed whereby the left arch was divided between the left common carotid artery and the left subclavian artery. In the third instance of successful surgery, reported by Sweet et al.[8] (Case 6), a patent ductus arteriosus was ligated and divided and then the left arch was ligated and divided between the left innominate artery and the stump of the divided ductus arteriosus. In one case of unsuccessful operation reported by Gordon[19] (Case 9), a clinical diagnosis of an aortic ring was made and thoracotomy was undertaken but no double aortic arch was discovered; at autopsy it was found that a double aortic arch was present but the relations of the two components were such that the smaller right arch was obscured by the larger left arch which was at a higher level.

TABLE I

CASES REPORTED IN INFANTS (ARRANGED ACCORDING TO AGE)

Case No.	Author and Date Reported	Age	Sex	Symptoms	Pathologic or Operative Findings
1.	von Siebold[14] 1836	10 days	?	Cyanosis from birth, loud stertorous breathing, stridor, and difficulty in feeding. Died from exhaustion.	Complete transposition, auricular septal defect, patent ductus arteriosus, double aortic arch enclosing trachea and esophagus.
2.	Schleussing[15] 1925	1 mo.	M	Stridor (ascribed to thymus clinically). No other information given.	Double aortic arch, patent ductus arteriosus, patent foramen ovale, compression of esophagus and trachea. Right descending aorta.
3.	Buschendorff[16] 1917	6 wks.	M	Loud stertorous breathing, cyanosis during crying.	Large anomalous retro-esophageal vessel connecting 1st part of right subclavian artery with left descending aorta.
4.	D.L., 1st case in this report	2 mo.	M	Developed wheezy, noisy respirations and brassy cough following cold at 3½ wks. of age. Died of aspiration of formula.	Double aortic arch; large right retro-esophageal component, small left anterior arch with obliterated lumen at site of attachment to descending aorta. Left common carotid artery from right arch. Left subclavian artery arose blindly from fibrosed portion of left arch. Left descending aorta.
5.	Herbut and Smith[17] 1943 Herbut[18] 1943	2½ mo.	F	Increasing respiratory difficulty with severe episodes of dyspnea and cyanosis. Died on 2nd day after tracheotomy.	Double aortic arch with large right component and small left arch. Right arch 1.0 cm. and left arch 0.5 cm. diameter. Patent foramen ovale. Left descending aorta.
6.	Sweet et al.[8] 1947	3½ mo.	M	Paroxysmal cough, wheezing. Cyanosis during feeding.	Successful surgery. Large right aortic arch passing behind esophagus. Small left arch. Patent ductus arteriosus divided, then left arch divided between left innominate artery and stump of ductus. Left descending aorta.
7.	Gross[8] 1945	4 mo.	M	Cough, cyanosis and wheezing respiration.	Successful surgery. Left arch divided between left common carotid artery and left subclavian artery. Left descending aorta.
8.	Gordon[19] 1947	4 mo.	F	Three blue spells shortly after birth, noisy respirations; cough, fever, marked stridor for 5 days. Compression left bronchus. Died from atelectasis and tracheal compression.	Atelectasis of 3 lobes of lungs with emphysema of other 2 lobes, early bronchopneumonia, trachea collapsed. Double aortic arch, size not measured. Left descending aorta.[20]
9.	Gordon[19] 1947	4 mo.	M	In oxygen after birth. Noisy respirations worse on feeding or lying down. Attacks of cyanosis. Marked stridor. Compression of trachea on bronchoscopy. No abnormality on barium swallow. Lipiodol suggested tracheal constriction.	Exploratory thoracotomy—no vascular ring. Died 3 days later, following severe cyanosis, from asphyxia. At autopsy double aortic arch, left arch larger, right arch at lower level and obscured by higher left arch. Left descending aorta.[20]
10.	Gordon[19] 1947	4 mo.	F	Two cyanotic attacks shortly after birth. Persistently noisy breathing. Regurgitation of feedings. Cough, fever, respiratory distress, diarrhea. Died from atelectasis.	Double aortic arch, right arch larger. Patent ductus arteriosus from left arch. Atelectasis of right upper lobe and emphysema of left lung. Left descending aorta.[20]
11.	Wolman[3] 1939	4½ mo.	M	Stridor since birth, hoarse cry, paroxysmal cough, terminal cyanosis. Died from bronchopneumonia.	Double superior vena cava, left superior vena cava crossed posteriorly to enter coronary sinus. Double aortic arch. Left arch 6 mm. and right arch 8 mm. in diameter. Left descending aorta.

TABLE I (Continued)

Case No.	Author and Date Reported	Age	Sex	Symptoms	Pathologic or Operative Findings
12.	Gross and Ware[7] 1946	5 mo.	F	Cough, cyanosis, stridor and dysphagia.	Successful surgery—left arch divided between left common carotid artery and left subclavian artery as in Case 7. Left descending aorta.
13.	Ewald[21] 1926	5 mo.	M	Cough and dyspnea since birth aggravated by crying. Died of inanition and bronchopneumonia.	Double aortic arch. Left arch stenosed between left subclavian artery and blind retro-esophageal pouch. Obliterated ductus arteriosus from blind pouch. Aorta decended on right.
14.	Snelling and Erb[22] 1933	5 mo	F	Constantly audible inspiratory stridor since birth aggravated by excitement, crying and feeding; brassy cough. Died from bronchopneumonia.	Double aortic arch, equal in size, 1.5 cm. in circumference. Left descending aorta.
15.	Herrmann[23] 1928	0 mo.	F	Cyanosis briefly at birth and terminally; stridor, cough and weight loss. Died of bronchopneumonia.	Double aortic arch with ductus from left arch. Right arch 8 mm. and left arch 7 mm. in diameter. Trachea constricted from 10.5 mm. above arch to 7.5 mm. in diameter in region enclosed by arch. Left descending aorta.
16.	Schall and Johnson[24] 1940	0 mo.	F	Noisy breathing, cough, cyanosis, hoarseness, and extension of head. Died from hemoptysis following erosion of trachea by right aortic arch.	Double aortic arch, patent foramen ovale, intrapulmonary hemorrhage. Trachea and esophagus enclosed but only trachea constricted. Arches equal in size, 1.3 cm. circumference. Subclavian and common carotid arteries arose separately from each arch.
17.	Crystal et al.[25] 1947	12 mo.	M	Wheezing and difficult breathing since birth, crowing and stridor, recurrent respiratory infections, apneic attacks and convulsions.	Died following unsuccessful exploration for double aortic arch. Double aortic arch not recognised at operation. Atretic ductus arteriosus divided. Arches about equal in size. Left descending aorta.
18.	Harris and Whitney[26] 1927	19 mo.	M	Cyanotic from aged 4 mos., dyspnea, convulsions, loss of consciousness. No symptoms referable to double aortic arch. Died on 3rd day of coma following convulsion.	Right aortic arch with small retro-esophageal left arch, patent ductus from left arch. Right descending aorta. Nonfunctioning left ventricle with ventricular septal defect. Both aorta and pulmonary artery arose from right (anterior) ventricle. Anomalous venous return to heart.
19.	Gordon[19] 1947	20 mo.	F	No symptoms referable to double aortic arch. Died from bacillary dysentery, acute peritonitis and bronchopneumonia.	Patent ductus arteriosus. Double aortic arch an incidental finding. Relative sizes not stated. Left descending aorta.[19]

The patient of Crystal et al.[25] (Case 17) died several hours after exploration for a double aortic arch. At operation only an atretic ductus arteriosus was divided; the double aortic arch was not recognized owing to an unusually high attachment of the pericardium.

The outcome in infants is in marked contrast to that in the older patients listed in Table II. With the exception of the first six patients, all lived to be 39 years or older and only three had symptoms referable to the double aortic arch. Of these three, the first two (Cases 20 and 21)[8,9] had symptoms from infancy and underwent successful surgery at the ages of 4 and 9 years, respectively. The third, Welch's patient (Case 28),[30] was the only one who later in life developed symptoms attributable to constriction of the trachea; in this instance the onset of symptoms was due to the development of an

TABLE II

CASES REPORTED OVER TWO YEARS OF AGE (ARRANGED ACCORDING TO AGE)

Case No.	Author and Date Reported	Age (Yrs.)	Sex	Remarks	Pathologic or Operative Findings
20.	Sweet et al.[8] 1947	4	M	Observed from aged 9 mos. Cough, vomiting, noisy breathing, fever, repeated respiratory infections. Liquids and strained foods only. Tracheotomy followed by tracheo-esophageal fistula and gastrostomy.	Successful surgery at 4 yrs. Large retro-esophageal left arch giving off left common carotid and left subclavian arteries then right innominate artery. Small right arch from left ascending aorta to right descending aorta grooving right bronchus. Right arch divided.
21.	Steinberg[9] 1948	9	M	Observed from aged 3 mos. Difficulty in breathing since birth, hoarseness, intermittent cyanosis; exercise intolerance, rasping cough, dysphagia. Repeated respiratory infections. Tracheal compression on bronchoscopy, posterior indentation of esophagus with barium, narrowing of trachea with lipiodol.	Successful surgery at 9 yrs. Large right retro-esophageal arch. Small left arch represented by small vessel from left subclavian artery to left descending aorta. Left arch divided. Ligamentum arteriosum divided.
22.	Bertin[27] 1824	12	?	No history available.	Left arch smaller than right. Aorta descended on left.
23.	N.P., 2nd case in this report	20	F	No symptoms referable to double aortic arch. Sudden death on 15th postoperative day following a right subclavian to pulmonary artery end-to-side anastomosis.	Tetralogy of Fallot with double aortic arch. Left arch larger and passed behind esophagus to join smaller right aortic arch and form right descending aorta. Questionable ball thrombus in left ventricle.
24.	Blackford[28] 1928	24	M	No symptoms referable to double aortic arch. Clinical diagnosis was aneurysm right subclavian artery. Died of pneumonia following operation.	Coarctation of aorta. Patent vestigial right dorsal aorta 14 mm. circumference from right subclavian artery passing behind esophagus to left descending aorta—possibly an anomalous collateral artery.
25.	Kotljartschuk[29] 1934	29	F	No symptoms referable to double aortic arch.	Left arch half the size of right arch. Left descending aorta.
26.	Blincoe et al.[3] 1936	39	M	No dysphagia or dyspnea B.P. 150/90	Double aortic arch, equal in size. Left arch 4.75 cm. and right arch 4.8 cm. in circumference. Left descending aorta.
27.	Herbut[18] 1943	39	M	Died from classical Addison's disease. No symptoms referable to double aortic arch.	Double aortic arch. Right arch 1.8 cm. and left arch 1.2 cm. in diameter. Left descending aorta.
28.	Welch[30] 1891	43	M	Six months prior to death developed paroxysmal cough, hoarseness increasing to aphonia, dyspnea. Symptoms attributable to aneurysm.	Double aortic arch enclosing trachea only. Aneurysm size of hen's egg at site of origin of right common carotid artery. Left arch larger than right. Left descending aorta.
29.	Hamdi[11] 1906	45	M	No symptoms.	Double aortic arch, left smaller than right. Left descending aorta.
30.	Arkin[5] 1936	46	M	Double aortic arch diagnosed during life. Died of hemorrhage from gastric carcinoma. Dysphagia and vomiting attributable to carcinoma. Syphilitic infection also.	Right aortic arch passed behind esophagus to descend on left. Fibrosed area between side of left subclavian artery and diverticulum of descending aorta.
31.	Brigham[32] 1922	50	M	Dissecting room specimen. No symptoms.	Double aortic arch. Left arch fibrosed posteriorly distal to origin of subclavian artery. Left descending aorta.

TABLE II (Continued)

Case No.	Author and Date Reported	Age (Yrs.)	Sex	Remarks	Pathologic or Operative Findings
32.	Arkin[4] 1926	50	M	No symptoms referable to double aortic arch. First case to be diagnosed during life by fluoroscopy. Death from periarteritis nodosa.	Pathology of arch similar to Case 30 (Arkin,[5] 1936).
33.	Hurley and Coates[33] 1927	53	F	Died of cerebral hemorrhage. Dissecting room specimen.	Double aortic arch. Left arch obliterated between left common carotid artery and left subclavian artery. Aorta descended on left.
34.	Heller[34] 1904*	54	F	No symptoms.	Right arch 3.5 cm. and left arch 4 cm. circumference. Left descending aorta.
35.	Roschdestwenskij[36] 1929	55	F	Pain in chest and dyspnea for 3 yrs.; dysphagia for 3 mos. Luetic aortitis. Cause of death not stated.	Double aortic arch. Right arch 10.8 cm. and left arch 9.2 cm. circumference. Aorta decended on left.
36.	Dittrich[37] 1886	56	F	No symptoms referable to double aortic arch. Died of peritonitis and pelvic abscess.	Double aortic arch. Right arch 2.5 cm. and left arch 1.6 cm. in diameter. Left descending aorta.
37.	Issajew[38] 1931	65	M	Dissecting room specimen.	Right aortic arch with aneurysmal dilatation posteriorly extending behind esophagus. Fibrous band from this dilatation to left common carotid artery. Left subclavian artery and barely patent ductus arteriosus arose from retro-esophageal dilatation. Right descending aorta.
38.	Lockhart[39] 1930	67	M	Dissecting room specimen.	Double aortic arch. Right arch 5.5 cm. and left arch 7.4 cm. in circumference. Aorta descended on left.
39.	Watson[40] 1877	70	F	Dissecting room specimen.	Double aortic arch with obliterated fibrous band from left subclavian artery to ligamentum arteriosum. Aorta descended on left.
40.	Schilling[41] 1932	75	M	Dissecting room specimen.	Right aortic arch passing behind esophagus. Left arch obliterated between left subclavian artery and blind pouch which communicated with descending aorta. Aorta descended on left.
41.	Curnow[42] 1874	87	F	No symptoms on swallowing or breathing.	Small left arch. Large right arch. Left descending aorta.
42.	Shaw[43] 1897	Adult	M	Dissecting room specimen.	Right arch 2.5 cm., left arch 1.0 cm. in diameter. Aorta descended on right to 8th dorsal vertebra then crossed to descend on left.

* This case was also described and reported by Neddersen.[35]

aneurysm at the site of origin of the right common carotid artery from the right aortic arch. Roschdestwenskij's patient (Case 35)[36] suffered from dysphagia but this may have been due to the complication of luetic aortitis.

The foregoing analysis indicates that when a double aortic arch causes symptoms of constriction, these symptoms will develop during the first two years of life. Furthermore, operation is indicated only in patients who display such serious symptoms. It cannot be stressed too strongly that the incidental finding of a double aortic arch is not an indication for surgical division of the arch.

It is worthy of note that in only two of the infants (Cases 4 and 13) was the left or anterior arch partly obliterated and fibrosed, whereas such was the finding in seven of the 23 older patients listed in Table II. This suggests that a pulsating vessel may cause more constriction than a fibrous cord. It also suggests that symptoms do not result from the process of obliteration of the arch. This conclusion does not agree with that of Blackford et al.[12] regarding the case reported by Jex-Blake[56] and commented on by Sir Arthur Keith of a puppy which had symptoms of esophageal obstruction due to a vascular ring formed by a right aortic arch and a ductus arteriosus. Their comment, which agreed with that implied by Sir Arthur Keith, was that "contraction of the ductus in the stage of its obliteration resulted in strangling the esophagus."

TABLE III

OTHER CASES OF WHICH THE ORIGINAL REPORTS WERE NOT AVAILABLE
(ARRANGED ACCORDING TO DATE OF ORIGINAL REPORT)

Case No.	Author and Date Reported	Quoted by	Remarks
43.	Hommel[1] 1737	Lockhart[19] Roschdestwenskij[28]*	Aorta encircled trachea and passed down on left side. Left arch smaller.
44.	Biumi[49] 1765	Poynter[45] Roschdestwenskij[28]	Left arch smaller than right. Aorta descended on left. Adult.
45.	Malacarne[50] 1784	Poynter[45] Roschdestwenskij[28] Lockhart[19]	Aorta divided 8 mm. from its origin into two separate ascending aortae enclosing pulmonary artery as well as esophagus and trachea. Five aortic valve cusps. Left descending aorta. Adult.
46.	Sagorskij[51] 1824	Roschdestwenskij[28] Blincoe et al.[2]	Trachea only enclosed by double aortic arch. Aorta descended on left. Adult.
47.	Thomson[52] 1863†	Brigham [53] Sprong and Cutler[54] Blincoe et al.[2]	No symptoms referable to double aortic arch. Left arch obliterated between left subclavian artery and origin of ductus arteriosus from retro-esophageal pouch. Aorta descended on left. Adult.
48.	Leboucq[47] 1894	Blincoe et al.[2]	Left arch smaller than right. Left descending aorta. Adult.
49.	Kajava[55] 1914	Sprong and Cutler[54] Blincoe et al.[2]	Asymptomatic. Left arch half the size of right arch. Left descending aorta. Adult.

* Roschdestwenskij also refers to cases reported by: (a) Hyrtl,[44] 1841, of a stillborn monster in which a large left arch descended on the left and a small right arch descended on the right as far as the 8th dorsal vertebra before crossing to the left (also referred to by Poynter[45] and Blincoe et al.[2]); (b) Cruveilhier,[46] 1843, in which there were 2 aortic arches and 2 descending aortae (also referred to by Poynter[45] and Leboucq[47]); (c) Klinz, 1905,[48] in which there was a double aortic arch, each component being at a different level. These cases are not included in this paper as there was no true vascular ring.

† In an article by Turner[52] in 1862, there is a description by Thomson of a case of double aortic arch. It seems probable that this is the same case as that ascribed to Turner by Sprong and Cutler.[54]

When the cases in all three tables are considered, it is found that a portion of the lumen of the left arch was obliterated in 10 cases. The obliteration was located between the left common carotid artery and the left subclavian artery in the cases described by Hurley and Coates (Case 33)[33] and by Issajew (Case 37).[38] In our first case (Case 4) the left subclavian artery arose from the obliterated portion of the left arch. The fibrous band was located between the subclavian artery and the descending aorta in the other eight cases. In no instance was any part of the lumen of a persistent right arch obliterated.

In the 33 cases in which both arches were recorded as patent, considerable variation was reported in their relative sizes. The arches were of approximately equal size in four (Cases 14, 16, 17 and 26); the left was larger in eight (Cases 3, 9, 20, 23, 24, 28, 34 and

38); the left arch was only slightly smaller in four (Cases 11, 15, 35 and 48). In 17 cases the left arch was appreciably smaller than the right component.

Of the remaining six cases out of a total of 49, no record is available as to the patency or relative sizes of the aortic arches.

It is noteworthy that out of 47 cases in which the position of the descending aorta is stated, the aorta descended on the right in only seven instances. In four (Cases 13, 18, 37 and 42) the right arch was the larger component, in two (Cases 20 and 23) the left arch was larger, while in the seventh (Case 2) no record is available of the size of the arches.

Further analysis of the cases in the series shows that it is the exception, not the rule, for an aortic ring to be associated with a malformed heart. Of the 47 cases previously reported, only two had a malformation of the heart and in each the malformation belonged to the persistently cyanotic group. Von Siebold's case (Case 1)[14] had a complete transposition of the great vessels. The case reported by Harris and Whitney (Case 18)[26] had a nonfunctioning left ventricle. Our patient, N. P. (Case 23), is a third instance of the occurrence of a malformation of the cyanotic group with a double aortic arch. Of these three, von Siebold's patient was the only one in whom there were symptoms referable to the double aortic arch (see Addendum).

Other vascular abnormalities have been described in association with a double aortic arch. Malacarne[50] reported an unusual case (Case 45) in which the aorta divided into two separate ascending aortae 8 mm. from its origin and surrounded the esophagus, trachea and pulmonary artery. In addition, the aortic valve had five cusps. Blackford[28] reported a coarctation of the aorta (Case 24) in which there was an aberrant artery which connected the right subclavian artery with the descending aorta below the site of the coarctation. Wolman's case (Case 11)[3] had two superior venae cavae. Welch[30] and Sagorskij[51] each reported one case (Cases 28 and 46, respectively) in which only the trachea was encircled by the double aortic arch. Our first case, D. L. (Case 4) was unusual in that the left common carotid artery came off the right aortic arch and the left subclavian artery originated blindly from the fibrotic portion of the left arch.

This series is too small to draw conclusions as to the sex incidence of double aortic arch. However, of the 42 patients listed in Table I and II, 24 were male and 16 were female; no record is available of the sex of the other two patients.

The suggestion that surgery may offer relief from symptoms was made previously in 1931 by Abbott,[57] in 1933 by Sprague and his associates,[13] and in 1943 by Herbut and Smith.[17] In 1945 Gross[6] published the first case report of successful division of a vascular ring caused by a double aortic arch. Four additional cases have since been reported.[7-9] In consequence of this advance, correct clinical diagnosis has become important. In addition, a new problem has arisen, namely, the selection of cases for operation.

As regards diagnosis, the first essential is to differentiate a simple right aortic arch without a retro-esophageal vessel from a right aortic arch with a retro-esophageal vessel. Only in the latter instance is there anterior displacement of the esophagus at the level of the aortic arch in the oblique views. If a retro-esophageal vessel is demonstrated, the second essential is to determine whether a vascular ring is present. Such a ring is difficult to distinguish from a right aortic arch which passes behind the esophagus to descend on the left.

A double aortic arch is one cause of a vascular ring. Arkin[5] and Paul[11] point out that where both arches are patent, the fluoroscopic findings are similar to those of a right aortic

arch with a retro-esophageal aorta (or diverticulum or subclavian artery), except that in addition a second shadow may be visible in front of the trachea in the oblique views.

Recently Neuhauser[58] has discussed the problems of diagnosis from the radiologic standpoint in his report of four cases, two proved at operation (reported separately by Gross[5] and Gross and Ware[7]). He cites the following as characteristic of a double aortic arch:

1. In the lateral projection there is narrowing and anterior displacement of the trachea at the level of the aortic arch.

2. With barium in the esophagus, a rounded pulsating mass is visible posterior to the esophagus which displaces the esophagus forwards.

3. In the antero-posterior projection with barium in the esophagus there is no deviation of the esophagus to the left as in cases of simple right aortic arch, but there is a narrowing of the esophagus from both right and left sides.

4. A similar deformity of the trachea is visible after the instillation of lipiodol; the trachea is displaced forwards at the level of the aortic arch and narrowed from both right and left sides.

Faber et al.[59] also consider that the esophagus is displaced to the left in a simple right aortic arch but appears uniformly constricted without deviation in the antero-posterior view in cases of double aortic arch.

The term constriction is used here to denote a uniform constriction from both sides and is not to be confused with the narrowing which results from indentation on one side only. In our opinion, the implication that there is always such a constriction without deviation of the esophagus is open to question. It is not in agreement with Arkin's original description[4,5] nor with the autopsy findings in two of his reported cases.* Furthermore, in our two proved cases of double aortic arch the esophagus was indented on the right with displacement of the esophagus to the left in our first case, D. L. (Case 4), whereas in our second case, N. P. (Case 23), the indentation was on the left and the esophagus was displaced to the right. Similar variations were present in Cases 6 and 20 reported by Sweet et al.[8] Nevertheless, a constriction of the esophagus, when present, is a most important diagnostic feature since it can only be caused by a vascular ring and thereby serves to differentiate this malformation from a simple right or left aortic arch with a retro-esophageal vessel.

It would seem that some of the cases reported during life as cases of "persistent right aortic arch" may well have had a right aortic arch with a retro-esophageal pouch and an obliterated isthmus representing a left aortic arch; i.e., in reality they may have been examples of a double aortic arch. As mentioned previously, such a possibility was advanced by Sprague et al.[13] in the report of their cases. Arkin[4] in 1926 emphasized that in a right aortic arch with a right descending aorta, a left aortic root should always be looked for behind the esophagus. Such a retro-esophageal pouch produces a forward dislocation of the esophagus but it is usually below the level of the right aortic arch. A similar appearance may be produced by a retro-esophageal right or left subclavian artery when it arises respectively from a left or right descending aorta. Another possibility, discussed by Abbott and Weiss,[60] is the origin of the ductus arteriosus from a right descending aorta. Yet another instance is that of a retro-esophageal vessel of collateral circulation in patients with congenital malformations of the heart of the cyanotic group.

* Arkin reported 6 cases diagnosed during life. At the time of his article only 2 of these had been proved at autopsy.

Perhaps, as suggested by Neuhauser,[58] angiocardiography may aid in the differentiation of these various possibilities.

The pertinent question, however, is the presence of a retro-esophageal vessel associated with symptoms in infancy. The incidental discovery of a double aortic arch in the absence of symptoms should occasion no alarm and requires no treatment. In the case of an infant suffering from stridor or dysphagia, the possibility of a double aortic arch should always be considered, and the patient should be fluoroscoped with the utmost care. In such an instance, where a right aortic arch with a retro-esophageal vessel is demonstrated and where other causes of stridor and dysphagia have been excluded, an exploratory thoracotomy is indicated in the hope of relief of symptoms by division of a vascular ring. Before operation is undertaken, it is advisable to ascertain on which side the smaller component is located because it is the smaller component which can be more readily divided. Again it is emphasized, however, that only in patients who manifest serious symptoms is operation indicated. The mortality rate of operation is high at present—two patients out of seven have died. However, in neither instance of unsuccessful operation was the vascular ring divided. For those patients in whom one component of a double aortic arch has been divided, the immediate prognosis is good. As yet it is too early to determine the ultimate outcome. Exploratory thoracotomy without division of a ring has proved dangerous and therefore operation should not be undertaken unless it is justified by the severity of the symptoms.

Summary

The anatomic nature of a double aortic arch is described. Reference is made to the history of the malformation. The clinical picture and radiographic findings described by various authors are discussed.

Two cases are reported which demonstrate two types of double aortic arch. One, a relatively common type, had a large right arch with a retro-esophageal component and a left descending aorta; the second, a rare type, had a large left arch with a retro-esophageal component and a right descending aorta. Further, one was an infant who had symptoms of constriction whereas the other was an adult who had no symptoms referable to the double aortic arch.

Analysis is made of these cases and 47 other cases reported in the literature. This analysis reveals that:

1. There is a striking correlation between the occurrence of symptoms and the age and duration of life, but there is no correlation between the occurrence of symptoms and the type of double aortic.

2. A double aortic arch in which both components are patent throughout is more likely to produce symptoms than a double aortic arch in which one component is partially obliterated. The process of obliteration does not appear to give rise to symptoms.

3. There is considerable variation in the relative sizes of the components of a double aortic arch. The right component is usually the larger; part of the left component may be obliterated. To date, no case has been reported of obliteration of part of a persistent right component.

4. A double aortic arch occurs more commonly with a left descending aorta than with a right descending aorta.

5. It is unusual for a double aortic arch to be associated with a malformation of the heart. The association of a double aortic arch with other vascular abnormalities is less rare.

The two principal problems raised by the demonstration of a retro-esophageal vessel are discussed. The first concerns the nature of the malformation; the second concerns the advisability of operation in the given individual.

Addendum

Since this paper was submitted for publication two additional patients have been seen in the Cardiac Clinic, Harriet Lane Home, in each of whom a double aortic arch was proven at operation.

In one (R. W.), a boy aged 8 years, a diagnosis was made of tetralogy of Fallot with a right aortic arch, a right descending aorta, and a retro-esophageal vessel which was thought to be a left subclavian artery. There were no symptoms of constriction of the esophagus or trachea. At operation, a double aortic arch was found; the left arch was smaller than the right and passed behind the esophagus to join the larger right arch. The aorta descended on the right.

In the other patient (C. C.), a boy of 5 years, there was a history since infancy of some difficulty in swallowing and breathing in addition to symptoms of inadequate pulmonary blood flow. The clinical diagnosis was tetralogy of Fallot with a double aortic arch. At operation there was a small left anterior aortic arch which passed backwards to join a large right posterior arch and form a left descending aorta.

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SPANISH ABSTRACT

Doble Arco Aórtico; Reporte de Dos Casos y Revista de la Literatura

Se describe la naturaleza anatómica de un arco aórtico doble. Se hace referencia a la historia de la malformación. El cuadro clínico y los descubrimientos radiográficos descritos por varios autores son tratados.

Se reportan dos casos que demuestran dos tipos de arco aórtico doble. Uno, un tipo relativamente común, tenía un arco derecho grande con un componente retro-esófago y una aorta descendiente izquierda; el segundo, un tipo raro, tenía un arco izquierdo grande con un componente retro-esófago y una aorta descendiente derecha. Además, uno era un infante que tenía síntomas de constricción mientras que el otro era un adulto que no tenía síntomas referentes al arco aórtico doble.

Se ha hecho análisis de estos casos y 47 otros casos relatados en la literatura. Este análisis reveló que:

1. Hay una marcada correlación entre el suceso de síntomas y la edad y duración de vida, pero no hay correlación entre el suceso de síntomas y la anatomía específica del arco.

2. Un arco aórtico doble en el cual ambos componentes son patentes en todas partes es más probable que produzca síntomas que un arco aórtico doble en el cual un componente está parcialment obliterado. El proceso de obliteración no parece dar origen a síntomas.

3. Hay considerable variación en los tamaños relativos de los componentes de un arco aórtico doble. El componente derecho es generalmente el más grande; parte del componente izquierdo puede estar obliterado. Hasta la fecha no se ha reportado ningún caso de obliteración de parte de un componente derecho persistente.

4. Un arco aórtico doble sucede más communmente con una aorta descendiente izquierda que con una aorta descendiente derecha.

5. Es muy raro que un arco aórtico doble esté asociado con una malformación del corazón. La asociación de un arco aórtico doble con otras anormalidades vasculares es menos raro.

Los dos problemas principales presentados por la demostración de un vaso retro-esófago son tratados. El primero ataña la naturaleza de la malformación; el segundo la conveniencia de una operación en cierto individuo.

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UNILATERAL MULTICYSTIC KIDNEY IN INFANTS

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CYSTS of the kidney, of any type, are relatively uncommon. Those of greatest clinical significance are found in congenital polycystic kidneys. In that condition cysts are usually spread diffusely through the kidney and the condition is almost invariably bilateral. The cysts are thought to be due to a failure of union between the secretory and collecting portions of the kidney unit. As the cysts enlarge and by pressure destroy the remaining functional kidney tissue, renal failure and uremia supervene and death ensues. The condition is occasionally manifest at birth, even to the point of having been reported as a cause of dystocia,[1] and in such cases renal tumor may be prominent. However, in the great majority of cases the disease is unsuspected until the advent of renal insufficiency in adult life.

Of other kidney cysts, the majority are described as incidental findings at post mortem. Most of the solitary cysts of the kidney which have been reported are of this type. Such cysts vary from microscopic size to those one or two centimeters in diameter. Occasionally several are found in one kidney. The contained fluid is usually serous, occasionally hemorrhagic. These cysts are without clinical significance. Braasch and Hendrick[2] state that "simple cysts are definitely a disease of adult life." Seventy-five per cent of the cases found were in patients in the fifth, sixth and seventh decades. Simple cysts were observed in only four patients who were less than 21 years old.

Chalkley and Sutton[3] found 10 reported instances of large solitary renal cysts in children and added one of their own. Others[4-6] have reported solitary renal cysts in children. Most of these cysts were asymptomatic and discovered only incidentally at operation or autopsy. When symptoms occurred, they were referable to the large size of the cyst or, more rarely, to infection in the cyst.

The condition with which the present report is concerned is apparently rare. Young and Davis[7] state that solitary cysts may be multilocular but report no cases in infants. Meland and Braasch[8] make similar general statements. The four patients to be reported here presented large tumors in the neonatal period and in the second patient, a premature infant born in this hospital, the tumor was observed to grow and cause distress by pressure on the abdominal viscera. In two of the instances reported, the correct diagnosis was made preoperatively.

CASE REPORTS

Case 1. W. G., a white male infant aged 3 wks., had left the hospital 8 days after a normal delivery. At home he was difficult to feed and vomited frequently. After 5 days, mother felt a mass in the baby's abdomen and he was readmitted to the hospital. At 3 wks. of age, he was sent to the Harriet Lane Home.

Examination revealed a somewhat undernourished infant whose only abnormality was an abdominal mass. The mass bulged the left flank sufficiently to be visible on inspection. It was a large, firm,

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rubbery, tensely cystic tumor filling the left side of the abdomen, attached to the posterior parietes and movable to a limited extent. Intestinal loops could be palpated anterior to the swelling.

Intravenous pyelograms (Fig. 1A) failed to show any dye on the left. Enough dye was seen on the right to show a kidney of normal size and shape. Dye appeared in the bladder almost at once. Intestines were displaced to the right by a mass occupying most of the left side of the abdomen. Barium enema showed the left side of the colon displaced to the right.

Laboratory Examinations: Urine: Sp. gr. 1.018, trace of albumen, microscopic examination—8-10 w. b. c. (child had been cystoscoped elsewhere) NPN 39 mg./100 cc., CO_2 combining power

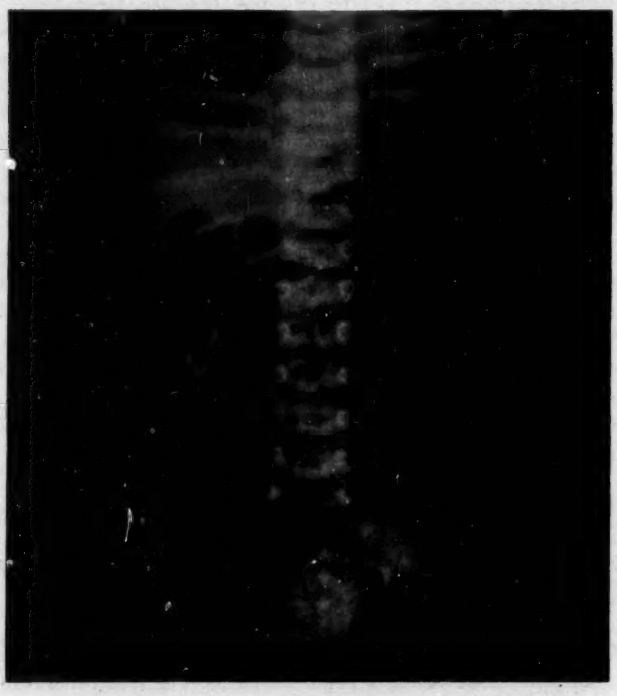

FIG. 1A. W. G., white male, aged 3½ wks. Intravenous pyelogram: Dye is visible in right kidney and in bladder. Intestines are displaced by mass filling most of left side of abdomen.

25.1 mEq./1., Ca 10.2 mg./100 cc., P. 7.0 mg./100 cc., phenol sulfonphthalein excretion, 35% in 1 hr., 65% in 2 hrs.

It was felt that the baby had a unilateral cystic kidney, causing symptoms by pressure.

Operation (M. M. R.): Peritoneal cavity was entered through a left transverse incision at the level of the umbilicus. Right kidney was normal in size and position. The mass was retroperitoneal, polycystic and in the position of the left kidney. Lateral peritoneum was incised and the descending colon reflected medially (Fig. 1B). To the upper medial surface of the thin-walled cysts which composed the mass was attached a small firm nodule of bluish tissue which appeared to be renal parenchyma. Entire mass was dissected free, its medial pedicle clamped, divided and ligated without search for any ureter and none was seen. Urinary output was unchanged after operation. NPN on the 7th and 9th day after operation was 39 mg./100 cc. and 40 mg./100 cc., respectively. Child did well postoperatively and was discharged the 10th day after operation. He is vigorous and well at this writing.

Pathologic Report: Specimen (Fig. 1C) is a mass composed of 7 thin-walled cysts varying in diameter from 2 to 5 cm. Linings are smooth and shiny and the septa between cysts, which do

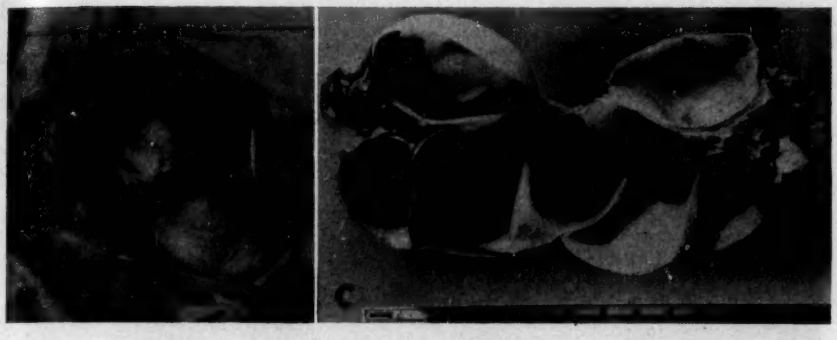

FIG. 1B. Operation: Descending colon has been freed from over cystic mass and displaced medially. Spleen and stomach are visible in upper and medial corner of wound.

FIG. 1C. Gross specimen, left kidney: Almost all of kidney has been replaced by large cysts but in this patient there is small fragment of recognizable renal tissue.

not communicate, are thin-walled and delicate. At 1 point is a small piece of recognizable renal tissue with cortical striations and papillae.

In the area appearing in the grosslike kidney one sees embryonal glomeruli (Fig. 1D) and greatly dilated tubules, none of these attaining the proportions of the cysts. On microscopic examination, the cyst walls are seen to be composed of dense laminae of collagen lined by a flat cuboidal epithelium (Fig. 1E). There is no renal tissue in the fibrous structure between the cysts.

Summary: At the age of 13 days, this infant was discovered to have a tumor in the left upper quadrant of the abdomen. Vomiting was the only symptom. At operation, when the baby was 3 wks.

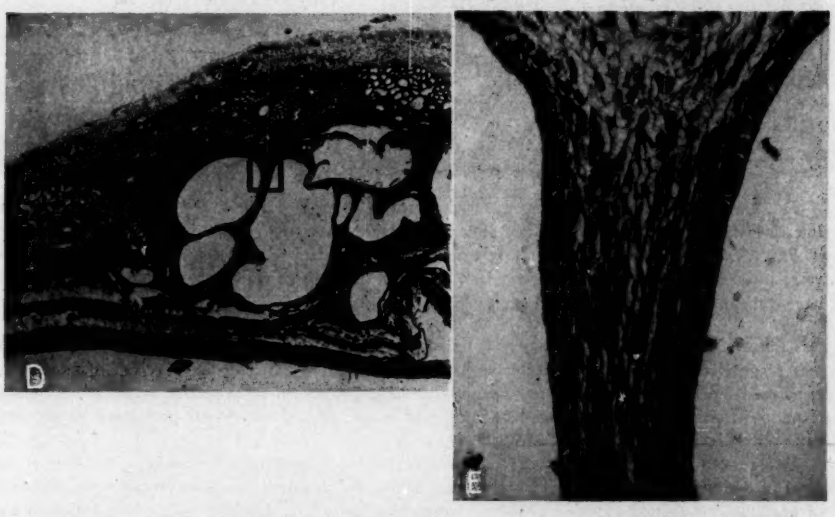

FIG. 1D. Photomicrograph (× 15) of section through solid fragment of specimen. Lining of large cyst is seen at bottom. Apparently solid tissue is honeycombed by smaller cysts and dilated tubular structures. There is occasional glomerulus-like structure in peripheral "cortical" layer.

FIG. 1E. Photomicrograph (× 250) of section indicated in box in D: Cysts are lined by flat cuboidal epithelium.

old, a multicystic mass was found replacing the left kidney. Baby has remained well since removal of the mass.

Case 2. J. T. was a Negro girl aged 7 wks. when operated upon. She was one of premature twins born Oct. 3, 1946, and remained in the obstetric nursery since she weighed 2230 gm. at birth. At about the 18th day of life, she began to take feedings poorly and became disturbingly distended. After the distention had been relieved, a large, firm, tensely cystic, lobulated mass could be felt occupying most of the left side of the abdomen from the costal margin to the iliac crest. A roentgenogram (Fig. 2A) showed the intestines displaced by a mass which filled the left side of the abdomen. It

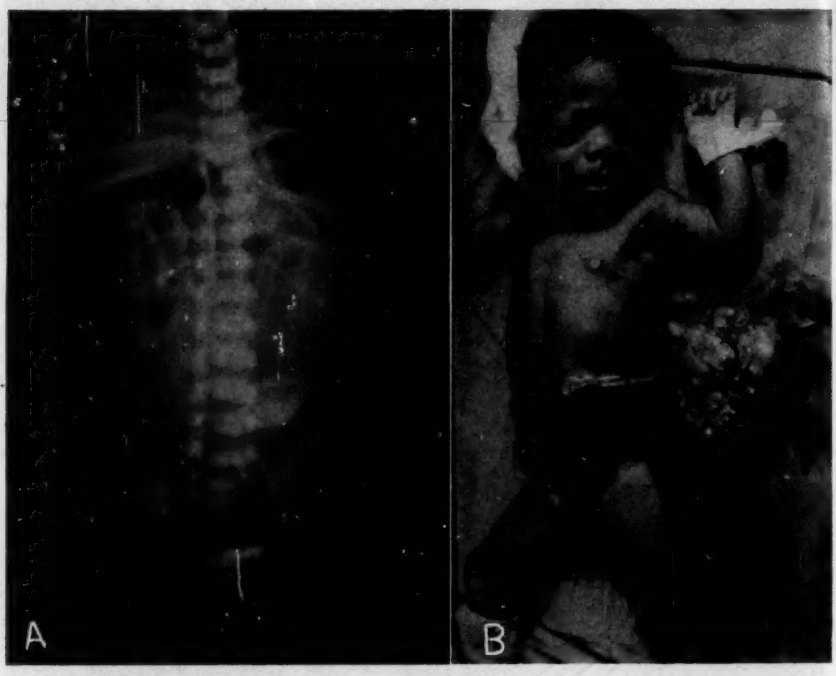

FIG. 2A. J. T., Negro female, aged 7 wks. Intravenous pyelogram: Dye is seen only in bladder. Intestines are displaced from left side of abdomen by large mass.

FIG. 2B. Baby and cyst on operating table immediately after drapes have been removed. Transverse incision has been closed subcuticularly and then sealed with collodion. Cyst seems too large to have come out of this infant's abdomen.

was felt that this was a cystic kidney and, the remainder of the examination being negative, operation was planned when the baby should have gained a little in wt. During the next few wks. she was transfused repeatedly and gained in strength and vigor but occasionally became distended. It became clear to all observers that the mass was increasing in size and operation was performed on the 54th day of life when the baby weighed 3160 gm.

Operation (M. M. R.): Peritoneal cavity was entered through a left transverse incision at the level of the umbilicus. Right kidney was normal in size and position. The mass proved to be composed of multiple cysts bound together by fibrous tissue. It occupied the entire left side of the abdomen and crossed the midline. Tumor arose retroperitoneally and presented through the mesentery of the descending colon, only a small portion of it being lateral to the colon. By careful dissection, it was possible to peel away the colon and mesocolon and leave the multicystic tumor exposed. There was a definite pedicle with vessels and a delicate white, elastic structure which was taken to be ureter. On division it retracted and could be traced to a ureter-like structure passing down to the bladder.

FIG. 2C. Gross specimen, left kidney: Collapsed cysts are supported by tooth picks. Kidney is replaced by large cysts.

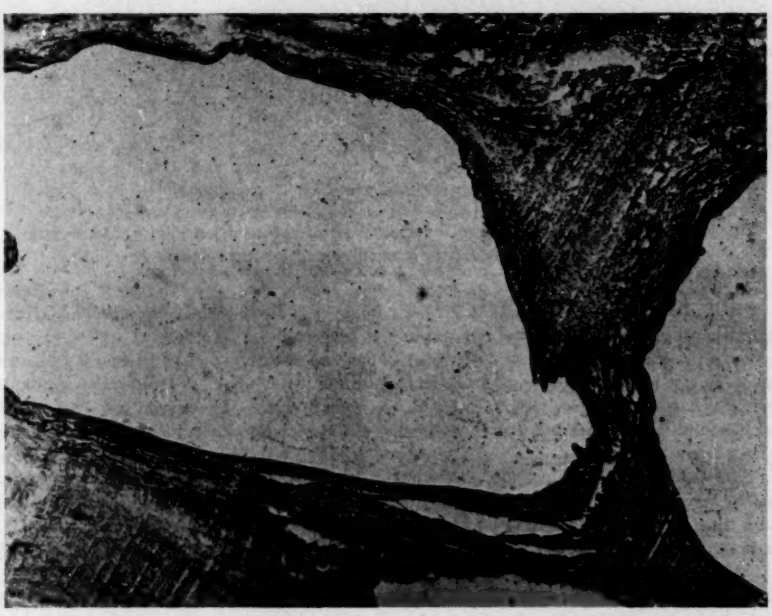

FIG. 2D. Photomicrograph (× 30) showing flat cyst lining and amorphous fibrous tissue between cysts.

Tumor was removed with no difficulty although it seemed almost as large as the child's entire abdomen (Fig. 2B). Adrenal was dissected off and left intact.

Child was discharged from the hospital in good health 11 days after operation. She then weighed 3190 gm. She is vigorous and well at this writing.

Pathologic Report: Specimen is a multiloculated cystic structure 9 cm. in greatest diameter. It is composed of large and small cysts held together by dense fibrous tissue. No renal tissue is recognized and on cut section (Fig. 2C) little or no solid tissue is seen. Lining of the cysts is shiny, white

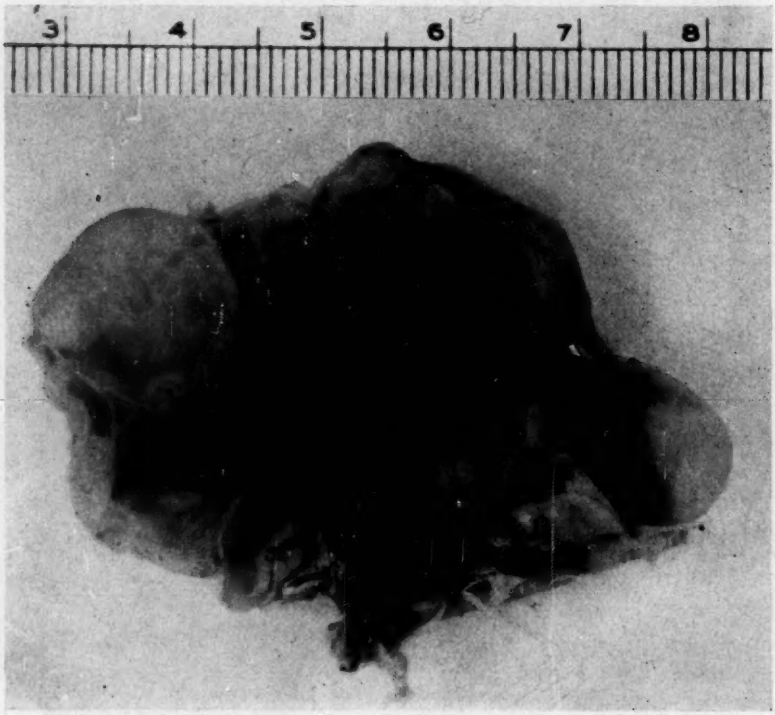

FIG. 3A. R. McC., Negro female, aged 1 mo. Gross specimen of left kidney: Dozen large cysts replace kidney entirely. There is small amount of spongy tissue in middle.

and smooth. Under the microscope (Fig. 2D) the lining cells are seen to be low cuboidal. Here and there occasional glomeruli and dilated tubules are seen between the cystic spaces.

Summary: A premature Negro girl developed abdominal distention and at the age of 18 days was found to have a left upper quadrant mass. Increasing size of the mass led to operation on the 54th day of life. A multicystic mass was found replacing the left kidney. Ureter was a solid cord. Occasional glomeruli and tubules between the cysts were the only traces of renal structure. Baby has been well since removal of the mass.

Case 3. R. McC., a Negro girl, died at the age of 1 mo. Only the autopsy record is available. She is said to have had diarrhea for 2 wks. and to have died 6 hrs. after admission to the hospital. The features were thought to be mongoloid. Chief interest in the autopsy centered in the left kidney, the right being normal. Position off the left kidney was occupied by a large, lobulated mass twice the size of the right kidney.

Pathologic Report: Gross examination: Left kidney is replaced by a number of noncommunicating cysts, 12 being seen in the cut section (Fig. 3A). There is a little spongy tissue in the central portion

between the cysts. Pelvis cannot be identified. Upper third of the ureter is a tiny, transparent cord. Below, it takes on more the appearance of ureter but is still small with a questionable lumen. Left ureteral orifice can be entered with a probe which passes upward only a few millimeters.

Microscopic examination: Left kidney is almost entirely occupied by many large, thin-walled cysts. Only a few abnormal glomeruli and dilated tubules can be found and these are in the spongy central section described above (Fig. 3B). The cysts are lined by flat cuboidal epithelium and separated by dense connective tissue devoid of epithelial elements (Fig. 3C).

Summary: Autopsy specimen from a 1 mo. old infant dead of diarrhea shows a left kidney almost identical with those in the operative Cases 1 and 2.

FIG. 3B. Photomicrograph (× 40) of section through spongy area. Note thick walled cysts and few clusters of distorted tubular structures in mass of amorphous fibrous tissue.

Case 4. P. A. N., a white girl aged 6 wks., was admitted to the hospital in acute distress due to a retropharyngeal abscess. This was successfully treated and during the infant's convalescence a tumor was palpated in the left upper quadrant.

Operation (Dr. W. P. Longmire): Peritoneal cavity was opened through a left transverse incision. Right kidney was normal. Left kidney was replaced by a multicystic mass. Descending colon was reflected and the retroperitoneal cystic tumor exposed and resected. There was a vascular pedicle medially, but no suggestion of any ureter. Child convalesced uneventfully and was discharged well 4 wks. later.

Pathologic Report: Gross description: Specimen consists of a multicystic kidney weighing 65 gm. and measuring 8 x 5 x 4 inches. There is no recognizable kidney tissue and no ureter. Tumor is composed of a mass of grape-sized cystic areas, each a thin-walled cyst filled with a clear light yellow fluid (Fig. 4A). Ureter is a mass of more solid tissue.

Microscopic Note: The large cystic areas have muscular walls lined by a single layer of rather flat epithelium. The more central solid portion of the mass contains scattered bits of renal tissue, some fairly normal, some immature (Fig. 4B). In addition, the solid areas contain many groups of tubules of large size, lined with columnar epithelium. Some of these tubules occur in groups. In 1

section (Fig. 4C) there is a small piece of cartilage and in 1 section is what appears to be a ureter. There were no cellular tumor-like areas anywhere in the numerous sections studied.

Summary: A multicystic left kidney was successfully removed from a 6 wks.' old white girl in whom it had been accidentally discovered. The kidney was replaced by a honeycomb of cysts. The intercystic stroma contained more tubular elements than were seen in Cases 1, 2 and 3 and, in addition, a fragment of cartilage was noted.

Previously Reported Cases

Case A (Schwartz[8]). Patient was a male infant in whom an abdominal mass was discovered at the age of 4 mos. Operation was refused by the parents because the child seemed well. At the age of

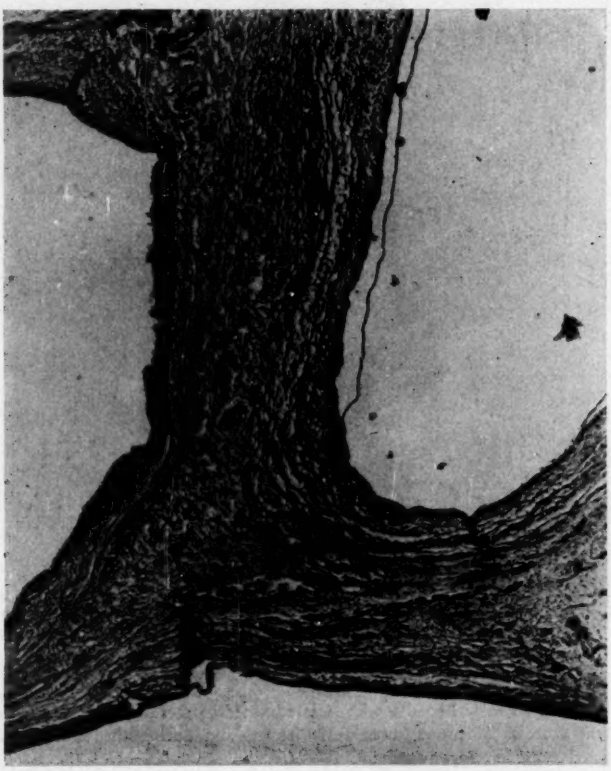

Fig. 3C. Photomicrograph (× 40) of section showing 3 adjacent cysts. Intervening material is dense connective tissue with no epithelial elements.

6 mos., the child was admitted to the hospital with pneumonia and studied after recovery. Entire left flank was filled with a soft nontender mass. Intravenous pyelograms showed a normal right kidney and there was no dye on the left after 2 hrs. Urine examination was negative. Cystoscopy failed to visualize a ureteral orifice on the left. Preoperative diagnosis of "hydronephrosis due to congenital stricture" was made and the patient operated upon at the age of 7 mos. Right kidney felt normal. Normal appearing pedicle and ureter on the left were divided and a large multicystic mass occupying the region of the left kidney removed. Specimen consisted of a normal ureter and a small amount of normal kidney tissue which had been compressed by many cysts ranging in size from a pea to an egg. They were held together with loose connective tissue. Definite calyces, pyramids or renal cortical

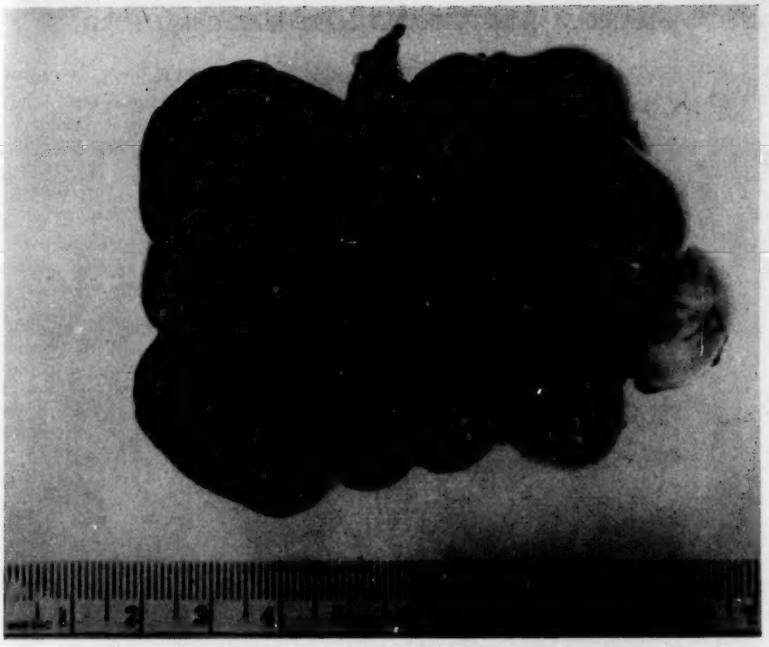

FIG. 4A. P. A. M., white female, aged 6 wks. Gross specimen of left kidney removed at operation. Grape-like cysts replace kidney.

FIG. 4B. Photomicrograph (× 40) of solid area showing several types of peculiar epithelial channels as well as margins of several large cysts.

tissue could not be identified. Walls of the principal cysts were composed of dense fibrous tissue and lined by a flat single layer of epithelial cells.

Child did well after operation and was alive and well 14 mos. later.

Case B (Campbell[8]). This patient is briefly mentioned. Photograph of the autopsy specimen shows multilocular cysts replacing the right kidney. The ureter was impervious. There was no pelvis and the calyces were absent. "The cysts developed in the cortical substance." The cause of death is not given and there is no description of the microscopic features. This is the only report of this condition by Campbell in his definitive work on pediatric urology.

FIG. 4C. Photomicrograph (× 40) showing another similar area in which there is island of unmistakable cartilage (= □). Histologic picture in this instance is different from that in Cases 1, 2 and 3 and suggests possibility of another type of malformation producing disorganized renal structure.

Case C (Lynch[28]). This infant was operated upon at 14 mos. At the age of 4 mos. she had been discovered to have a "hard and granular" left sided abdominal mass. Ascites was thought to be present. Operation for renal tumor was advised and refused. Two mos. later the family physician evacuated ascitic fluid. The mass grew steadily and when the child was 14 mos. old the parents requested operation. Laboratory studies revealed no abnormalities. At operation the right kidney appeared normal. The multicystic mass replacing the left kidney was removed. No ureter could be identified. Fourteen years later patient was well and a normally functioning right kidney was demonstrated.

Photographs show a kidney replaced by a honeycomb of numerous cysts of uniform size. No photomicrographs are presented and the pathologic description states, "The specimen was a multi-

cystic kidney in an advanced state of degeneration. The cysts contained straw-colored fluid. There was no normal renal tissue present nor was any tumor tissue demonstrable. The organ was filled with large multilocular cysts. It did not resemble a polycystic kidney grossly or microscopically."

Case D (Wakeley[11]). Patient was a 20 mos. old male infant admitted with a large abdominal tumor which had been discovered a few months after birth. The mass filled the entire right side of the abdomen. Urine was negative except for occasional white blood cells and red blood cells. Tumor had grown rapidly and caused some obstruction to the colon. Right nephrectomy was performed. Many aberrant renal vessels were noted and the kidney pelvis was dilated. Ureter was easily dissected free down to the brim of the pelvis, then ligated. Left kidney was normal.

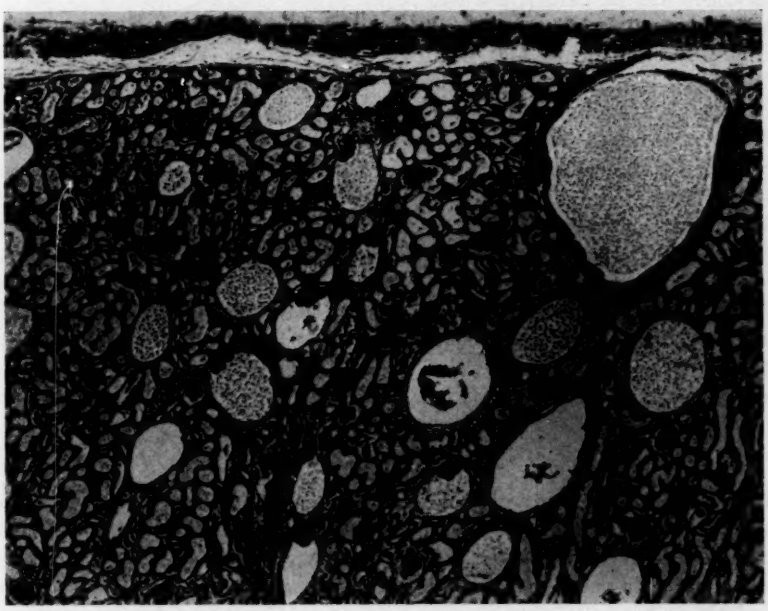

FIG. 5. Photomicrograph (× 40) of section from kidney of 9 mo. old baby dying of dysentery and found at autopsy to have bilateral congenital polycystic kidneys. Cortex is at top of photograph. Note that there is recognizable renal tissue but it is distorted and compressed by innumerable cysts. In many cysts glomerulus projects into lumen-like intracystic papilloma.

Pathologic Report: No normal kidney noted. The entire mass is made up of numerous cystic spaces, some containing fluid, others a colloid substance. Cysts are lined with epithelium which shows considerable variation, some being columnar while in other areas the cysts are lined with flattened cells resembling endothelial cells.

Case E (Mixter[12]). Patient was a 4 yr. old male admitted with acute onset of vomiting, and abdominal swelling of 4 days' duration. There were no urinary symptoms. A large mass was felt on the right side of the abdomen. A diagnosis of appendiceal abscess was made.

At operation, a large multicystic mass arising from the lower pole of the right kidney was found. Entire mass was grapefruit-sized. Nephrectomy was performed. No mention of pelvis or ureter is made.

Pathologic Report: "Nonmalignant cysts, probably arising from renal anlage."

Child recovered and was well only to die 1½ yrs. later with a volvulus around adhesions. At autopsy the left kidney was normal.

Case F (Kretschmer[13]). Patient was a 3 mos. old girl admitted because of intermittent vomiting and diarrhea since birth and failure to gain wt. Enlarged abdomen had been noted 3 wks. before

and an orange-sized, slightly tender mass felt in the right kidney region. Intravenous pyelograms revealed normal excretion on the left but no dye was noted on the right. Urine was negative. Preoperative diagnosis was tumor of the right kidney, probably malignant. At operation a lemon-sized cyst was found attached to the lower pole of the right kidney and several smaller cysts were seen in the kidney. Remainder of the kidney substance was normal. Nephrectomy was done. Patient developed bronchopneumonia and died. There are no photographs and no descriptions of the microscopic reports.

Thus, there are only six reports of patients with conditions similar to those herein reported. Of these six, Cases A and B of Schwartz[9] and Campbell,[6] respectively, are apparently precisely like our Cases 1, 2, and 3 in that one kidney was entirely replaced by several large cysts (or one multilocular cyst). Cases C and D reported by Lynch[10] and by Wakeley[11] had kidneys honeycombed by innumerable cysts replacing the kidney completely, much as in our Case 4. The appearance of histologically peculiar tubular structures and cartilage in our Case 4 suggested to the pathologist, Dr. Sam Blackman, that there was a teratomatous element in the production of the condition. In our four cases and in the first four cited from the literature, the process of organogenesis in one kidney seems to have gone completely awry. In none of them is there any semblance of renal architecture, cortical substance, papillae, calyces or pelvis, although a ureter-like cord was noted in several. This is very different from the condition obtaining in congenital polycystic kidney which is almost always bilateral and in which the fundamentally normal renal architecture is merely distorted by the numerous cysts (Fig. 5). In the Cases E and F reported by Mixter[12] and Kretschmer,[13] respectively, only a portion of the kidney was involved and this represents another condition, possibly a variant of solitary cyst.

Summary

Four infants are reported with unilateral replacement of the kidney by large cysts. These cases and six similar ones found in the literature show: (a) a large abdominal mass producing pressure symptoms only; (b) a normal contralateral kidney; (c) progressive increase in size of the mass; (d) adequate renal function after resection of the involved kidney.

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SPANISH ABSTRACT

Riñón Multicístico Unilateral en Infantes

Se reportaron cuatro infantes con reemplazo del riñon unilateral por quistes grandes. Estos casos y cuatro similares que se encontraron en la literatura muestran: (a) una gran masa abdominal que produce solamente síntomas de presión; (b) un riñón contralateral normal; (c) aumento progresivo en el tamaño de la masa; (d) adecuada función renal después de la resección del riñón complicado.

En nuestros cuatro casos y en los cuatro primeros citados de la literatura, el proceso de organogenesis en un riñón parece haber estado fuera de razón. En ninguno de ellos hay semejanza de la arquitectura renal, substancia cortical, papilas, cálices o pelvis, a pesar de que se notó un cordón parecido al uréter en varios. Esta es muy diferente de la condición que se obtuvo en riñón policístico congénito que es casi siempre bilateral y en el cual la arquitectura renal fundamentalmente normal es puramente deformada por los numerosos quistes.

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OCCURRENCE OF INNOCENT ADVENTITIOUS CARDIAC SOUNDS IN CHILDHOOD

By SIDNEY FRIEDMAN, M.D., WILLIAM A. ROBIE, LT. CMDR. (MC), USN, AND T. N. HARRIS, M.D.
Philadelphia

THE recent increase of interest in both congenital and rheumatic heart disease has re-emphasized the importance of a difficulty frequently encountered in the evaluation of the cardiac status of children, that is, the differentiation of those adventitious sounds which are of functional or physiologic origin from those which imply pathologic change. This differentiation is at times not easily made even with the aid of all the modern adjuncts available for cardiac diagnosis. In the effort to avoid overlooking a case of organic heart disease, there is a common tendency to attribute to such disease many adventitious sounds which may be functional or physiologic. The many cardiac neuroses and anxiety states which result have perhaps elevated the suffering derived from "iatrogenic"[1] heart disease to a level probably higher than that of organic heart disease itself. It was, therefore, considered of value to make a study of the innocent adventitious cardiac sounds of childhood under conditions which would closely simulate those encountered in general office practice.

Despite the appearance of many new and complicated technics for the study of cardiac status, auscultation remains the most commonly employed and readily available method for the detection of cardiac abnormality in childhood. Gibson[2] has recently stressed the relatively greater value of auscultation for cardiac diagnosis in the child as compared with the adult. Therefore, the basic criteria employed in this study for the differentiation of functional from organic adventitious sounds were those derived from cardiac auscultation. For this purpose, Levine[3] has frequently emphasized the importance of grading murmurs as to their intensity, the louder murmurs being attributed to organic changes. In childhood, however, this criterion is not uniformly valid, since many functional murmurs in this age group are relatively loud.[4] The thin thoracic and ventricular walls of childhood may contribute toward the improved transmission and detection of sounds. Ash[5,6] has stressed the importance of two other criteria for the evaluation of murmurs in childhood: location, or the point of maximal intensity, and the acoustic quality or character of these sounds. Midprecordial functional murmurs, if carefully ausculted, are rarely found to be loudest at the apex, but are almost invariably more prominent to the right of this point. The evaluation of the quality of murmurs requires a certain amount of training and experience. However, the high-pitched blowing murmurs of mitral insufficiency can, we believe, be distinguished in a high percentage of cases from the low-pitched, buzzing, vibratory, "twanging-string" murmurs heard so frequently over the mid-precordium in childhood. A recent phonocardiographic study by Harris, Friedman and Haub[4] has dem-

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onstrated on a physical basis the primary nature of quality as a criterion for the differentiation of blowing organic murmurs from the innocent variety in childhood.

Many estimations of the incidence of functional murmurs in childhood have been made in the past. Thus, in 1925, Thayer[7] reported the finding of systolic murmurs at the apex in 56% of individuals examined during the first decade of life. Fahr[8] estimated that 40 to 70% of all children between the ages of 4 and 14 years have systolic murmurs. Several other studies have tended to confirm this high incidence.[9-17] Extra heart sounds, such as the reduplicated second cardiac sound and the physiologic third cardiac sound, have also been found to occur with great frequency in the early age groups. In the present study, an attempt was therefore made to analyze these adventitious sounds by their qualitative as well as quantitative characteristics. Also, since little information is available concerning the method of production of functional and physiologic murmurs and cardiac sounds, an attempt was also made to correlate the incidence of these sounds with various possibly related factors, such as age, sex, state of nutrition, anemia and pulse rate.

Material and Methods

During the 1st 9 mos. of 1948, 500 children between the ages of 2 and 12 yrs. who attended the Medical Out-Patient Department of The Children's Hospital of Philadelphia were subjected to a special cardiac examination by at least 1 of the authors. Each patient was examined on only 1 occasion and the findings recorded on a special mimeographed form made for this purpose. Complete physical examination, medical history, tuberculin skin test and serologic test for syphilis comprised the minimal investigation performed on each patient in the clinic. Red blood cells of all Negro children were tested for sickling. Many of the subjects had been closely followed and studied over a period of several yrs. in the various clinics and wards of the hospital and thus were subjected to a host of other clinical evaluations and laboratory tests. Routine electrocardiography and cardiac fluoroscopy were not done at the time of examination. The average economic level of this group is undoubtedly low. The implications of this fact in the interpretation of the results of this study will be discussed later.

Patients were selected at random with no reference to age, color, sex or diagnosis, with the single exception that all patients with a history or physical signs suggestive of rheumatic fever, chorea, congenital heart disease or hypertension were excluded. Thus, the group did not include children suspected of having heart disease or children with illnesses such as severe sickle-cell anemia or Cooley's anemia, which could give rise to cardiac signs. All adventitious sounds noted were, therefore, thought to be functional or physiologic in origin. While the great majority of these children attended the clinic for consultation concerning various illnesses, most of these were of a minor nature, such as could be treated on an outpatient basis and were therefore comparable to the illnesses of children who might be seen in pediatric office practice. In order to simulate more closely the composition of a group of children such as would be seen in pediatric office practice, a number of healthy children who were being seen for routine follow-up purposes were also included.

Each patient was examined in the erect and supine positions and again in recumbency following a period of exercise which consisted of 10 raise-ups from the supine to the sitting position without assistance. Presence or absence of adventitious sounds was recorded with regard to point of maximal intensity, transmission, pitch, intensity and quality. Pulse rate was counted before exercise and the cardiac rhythm was noted. Other information obtained concerning each subject was that of age, sex, color, ht., wt., temperature and a statement concerning the previous surgical removal of tonsils and adenoids. In a group of 109 of these patients, a determination of the hemoglobin level was made on the day of examination, using a photoelectric colorimetric method. The optimal wt. of each subject was calculated from his age and ht., using standard tables. Those children who were more than 10% above or below the standard wt. for their age and ht. were classified as overweight and underweight, respectively. A crude estimation of the state of nutrition was provided by this calculation. Wts. and hts. were taken with shoes and outer garments removed; the age taken was that at the nearest birthday. All temperatures recorded were taken rectally except in those children above 10 yrs. of age who were cooperative. In these, the oral temperature was obtained.

Results

Functional Murmurs:

Incidence: Of the 500 children examined in this study, 234, or 46.8%, were found to have systolic murmurs over some area of the precordium. All these were considered to be of a non-pathologic nature, using the criteria previously described. Of these murmurs, there were 182 (corresponding to 36.5% of the group) which were of greatest intensity in the midprecordium, that is, in the 3rd, 4th or 5th interspaces to the left of the sternum but definitely to the right of the apex. In 91 children (18.2%), murmurs were found which were loudest in the pulmonic area, that is, in the 2nd interspace to the left of the sternum. In a group consisting of 39 subjects (7.8%), 2 separate functional murmurs were found in the same child, each murmur with its own point of maximal intensity and characteristic acoustic quality. Each of these children had a murmur heard best in the midprecordium and another in the pulmonic area. Ten children were found to have murmurs loudest

TABLE I

Position	No. of Murmurs
1. Erect	101
2. Recumbent	199
3. Both erect and recumbent	98
4. Recumbent, but not in erect	128
5. Erect, but not in recumbent	5
6. Recumbent, additional murmurs heard only after exercise	42
7. Recumbent, disappearing after exercise	28

at the apex and 1 loudest at the aortic area, which by virtue of their quality characteristics were considered to be of no pathologic significance. Thus, in 234 children, a total of 273 murmurs were detected.

Quality: Those murmurs audible in the pulmonic area had almost uniformly a low-pitched blowing quality. On a few occasions, murmurs in this area were described as humming or rumbling. Similarly, nearly all of the midprecordial murmurs had a characteristic vibratory or buzzing acoustic quality at the point of maximal intensity. Several of the louder murmurs in this area were best described as being of a "snorting," "scraping" or "twanging" quality but, in all cases, the underlying vibratory effect could be identified. All these murmurs were of low pitch, in contrast to the typical high-pitched apical systolic blowing murmur of mitral insufficiency in acute rheumatic fever or rheumatic heart disease. There was a striking and almost constant correlation between the location and quality of the great majority of these functional murmurs; those audible in the pulmonic region were typically blowing and low-pitched, while the midprecordial variety were in almost all cases vibratory in quality.

Intensity: Of the 273 murmurs heard in this study, 85.4% were classified as barely audible, 14.1% were described as moderately loud and only 0.5% were considered to be very loud.

Transmission: Aside from the 10 murmurs which were best heard at the apex, a total of 39 other murmurs which had their point of maximal intensity in some other location over the precordium could be detected at the apex. Of these, 2 had their origin in the pulmonic region and 37 in various points in the midprecordium.

Position: An analysis was made of the frequency of murmurs when auscultation was carried out in the erect position, in the recumbent position and again in the recumbent position following a standard period of exercise. The results are summarized in Table I.

Age: Figure 1 demonstrates the incidence of functional murmurs discovered at various age levels. It may be seen that at the highest age included in this study, 12 yrs., no tendency has appeared for a decrease in incidence of these murmurs.

Sex: Murmurs were found to be present in 51.5% of the males examined and 42.2% of the females. This difference is not significant.

Color: Among the Negro children, 48% were found to have murmurs; among the white children, 44.5%. This difference is not significant.

Nutrition: In the group of children found to be 10% or more below the standard wt. for their age and ht., the incidence of functional murmurs was 54%; for those 10% or more above the standard wt., the incidence of murmurs was 50%. For the intermediate group with a more or less average nutritional state, the incidence of murmurs was similar, 46%. These differences are not significant.

Temperature: The temperature ranges observed in this study were, with a few rare exceptions, moderate. There was no correlation between the rate of occurrence of murmurs and variations in temperature. Among the patients with no murmurs, 19.5% had a temperature of greater than 37.8°C., whereas of the patients who demonstrated murmurs, 23% had a temperature of over 37.8°C.

Chronic Infection: The presence or absence of tonsillar and adenoid tissue was used as an approach to a possible index of chronic infection and was found not to be related to the incidence of murmurs in this study. Eighteen per cent of those patients without murmurs had undergone a tonsillectomy and adenoidectomy, while a similar percentage, 17%, of those with murmurs had experienced the same operation.

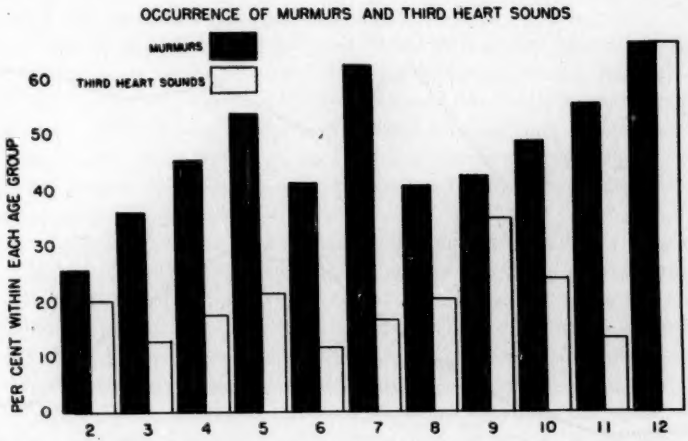

FIG. 1. Occurrence of cardiac murmurs and 3rd cardiac sounds in various age groups of children without known cardiac disease.

Pulse: The highest incidence of functional murmurs was found in those children with a cardiac rate of 90 beats/min. or less. Forty-nine and one-half per cent of children with such a cardiac rate demonstrated murmurs. In the pulse range of 90 to 110 beats/min., the incidence of functional murmurs was only slightly less, 47%. In those children with a pulse rate above 110/min., the incidence of murmurs was much lower, being only 22%.

Hemoglobin Level: The concentration of hemoglobin in the blood was determined in 109 patients. These values fell within a range of 6.5 to 14.5 gm./100 cc., the mean being 10.5 gm. Figure 2 demonstrates the incidence of functional cardiac murmurs at various hemoglobin levels and contrasts this relationship with the incidence of various hemoglobin levels in the group studied. The curve representing the former is relatively flat demonstrating a rather uniform incidence of murmurs at all hemoglobin levels, while the curve representing the number of patients falling into each hemoglobin level is bell-shaped, indicating a random distribution, with greatest frequency near the mean value. It is evident, then, that no correlation exists in these data between the incidence of such murmurs and hemoglobin levels in this range.

Extra Cardiac Sounds:

Incidence: In the 500 patients examined, a total of 157 extra cardiac sounds were detected in 137 (27.4%) patients. Several patients were found to have more than 1 such sound. One hundred children or 20% of the group demonstrated a physiologic 3rd cardiac sound; 34 (6.8%) showed a reduplication of the 2nd cardiac sound; 20 (4.0%) showed a reduplication of the 1st cardiac sound,

and a midsystolic click could be heard in 3 children, 0.6%, of the group. Figure 1 also shows graphically the incidence of the physiologic 3rd cardiac sound at various age levels. These sounds do not appear to occur in any 1 age group with particular frequency.

Location: The physiologic 3rd cardiac sound was best heard at the apex or slightly to the right of this point. Reduplication of the 2nd cardiac sound was almost invariably heard best in either the pulmonic area or along the left sternal border. Reduplication of the 1st cardiac sound was best recognized at the apex. The 3 midsystolic clicking sounds were heard in the midprecordium.

Relation of Extra Heart Sounds to Functional Murmurs: A degree of association was observed between the occurrence of functional murmurs and the other adventitious cardiac sounds. In those children with functional murmurs, extra cardiac sounds were detected in 34.2% of the cases, while in children with no functional murmurs the incidence of adventitious sounds was only 21.5%. Among the 100 children with physiologic 3rd cardiac sounds, 28.3% also had functional murmurs, while only

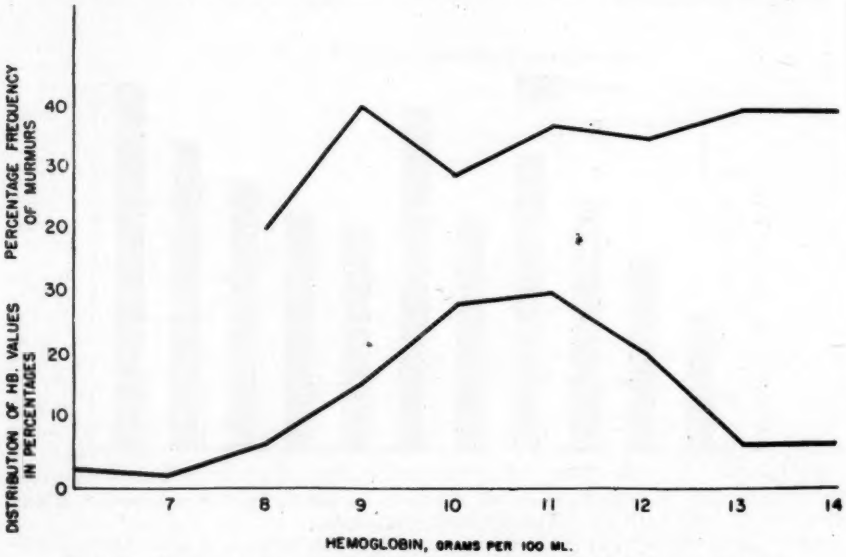

FIG. 2. Distribution of values of hemoglobin, in gm./100 ml., among children studied, and occurrence of murmurs within each group of this distribution.

13.1% fell in the no-murmur group. This same preponderance of extra cardiac sounds in the functional murmur group was present among those patients with reduplication of the 2nd cardiac sound and reduplication of the 1st cardiac sound, although to a slightly smaller extent.

Relation of Extra Heart Sounds to Other Factors: The relationship of the incidence of extra cardiac sounds to such factors as age, sex, color, nutritional state, temperature, chronic infection and pulse rate was also analyzed. No correlations could be detected except a tendency for an increased incidence of extra cardiac sounds when the cardiac rate was lower.

Miscellaneous: In all of the 500 children examined, the cardiac rhythm was found to be either normal sinus rhythm or sinus arrhythmia. In 2 instances, extra-systoles were heard. No murmurs were audible primarily in the tricuspid area despite careful auscultation in that region of the precordium.

DISCUSSION

Critique of the Group Studied

It is essential to consider the method of examination and the composition of the study group in order to evaluate the influence which these factors play upon the results obtained.

Since 70.5% of the children studied belong to the Negro race and the entire group consisted of clinic patients derived from a relatively low economic level, it might be reasoned that such children, having relatively poor nutritional states and associated low hemoglobin levels, might for these reasons tend to show an incidence of functional heart murmurs greater than that which would be found in the general population. This deduction stems from the fact that decreased blood viscosity contributes toward increased turbulence of blood flow[18] and might thereby favor the finding of more murmurs in those individuals with a poor nutritional state and an associated anemia. On investigating this possibility, it was found that the incidence of murmurs among those children who were more than 10% below standard weight for their age and height was not significantly different from that of the overweight or average weight groups. Also, variations in hemoglobin levels within the moderate ranges observed in this study did not appear to be correlated with the incidence of functional murmurs.

It might also be argued that the incidence of murmurs among patients seeking advice for specific complaints might be greater than in a group of "normal, healthy" children. However, the incidence of murmurs discovered among those children with a temperature elevation above 37.8° C. was found to be almost identical with the incidence in the normal temperature group. Similarly, no difference was noted among those with a history of tonsillectomy and adenoidectomy as compared with those who had these commonly infected tissues in situ.

Another factor which might tend to increase the number of murmurs detected would be the emotional disturbance associated with a hospital visit and a physical examination. It cannot be denied that in many instances this factor played an important role. However, this study showed a tendency for a lower incidence of murmurs in patients with pulse rates above 110 per minute. Also, the factor of emotional disturbance would be at least as common among patients seen in office practice as in this clinic group.

Thus, inherent in the method of this study, there are several factors which might have a tendency to increase the number of murmurs detected above the true rate, although the respective correlations fail to reveal such a trend. However, there are also factors which might be expected to have an effect in the opposite direction. The evanescent nature of functional murmurs is well recognized. By examining each patient on only one occasion, the incidence of murmurs found is that for one given time. If repeated examinations were made of each child over a prolonged time interval and under varied circumstances, the incidence thus derived would undoubtedly be higher, but would represent the potential incidence rather than the rate of occurrence of functional murmurs at any particular time. Similarly, the use of more vigorous exercise might be expected to demonstrate murmurs more frequently. The nature and amount of exercise employed in this study were arbitrarily selected because of their simplicity and practicability.

In a group of this size, selected at random, one might expect to discover a maximal incidence of organic heart disease of less than 3%, according to the estimate of White.[19] Although every practicable method, aside from electrocardiographic and fluoroscopic studies, was carried out in an attempt to eliminate children with heart disease, it is impossible to say that some of the murmurs might not, in fact, have been due to organic heart disease. However, even if the entire estimated 3% of cases of such disease had escaped detection, this percentage would hardly be sufficient to distort the results of this study.

Thus, the net result of all possible theoretic considerations which might increase or

decrease the likelihood of functional murmurs in this study is not only small but, in addition, the factors tend to counterbalance each other. Therefore, it may be assumed that the results of this study are approximately applicable to the general population in this age group.

Clinical Considerations

The detection of innocent adventitious cardiac sounds in over one half of the children in this study group emphasizes strongly the importance of careful cardiac auscultation in pediatric practice. The absence of pathologic significance of these sounds does not in any way detract from their clinical importance, since attendance at any cardiac clinic will demonstrate strikingly the frequency with which innocent adventitious sounds are improperly interpreted. The lack of a specific test to aid in making the diagnosis of rheumatic fever magnifies the importance of this point. A false diagnosis of organic heart disease in childhood is not uncommon under such circumstances and results in unnecessary suffering for both parents and child.

One is also struck by the almost uniform association of the quality of functional murmurs in childhood with the location of their point of maximal intensity on the precordium. With few exceptions, those murmurs best heard in the midprecordium possessed a characteristic vibratory or buzzing acoustic quality, while those audible in the pulmonic area were basically blowing or humming in nature. Using these criteria as a guide in association with intensity, pitch, transmission, etc., the identification of functional murmurs is markedly facilitated. Undoubtedly, a certain number of murmurs heard near the apex are of such indistinct quality that a definite differentiation cannot be made on this basis, but these constitute a small minority.

The apical location and transmission into the axilla of murmurs is classically considered an important criterion, in the differentiation of organic from functional murmurs. Of the 182 midprecordial murmurs, 37, or 20.3%, were audible at the apex. Nearly all these were best heard to the right of the apex, but many could be heard distinctly at the apex, the location which is characteristically occupied by the murmur of mitral insufficiency in acute rheumatic fever. However, in every case, careful auscultation revealed that these sounds were best heard at points to the right of the apex, and the detection of sounds at the apex represented the diffusion of sounds which were of maximal intensity at another locus. Similarly, two functional murmurs best heard in the pulmonic region were also audible, but with relatively much diminished intensity, at the apex. On careful auscultation it was easily established that the source of this sound was derived from the base of the heart. Thus, the fact that a murmur is audible at the apex or even to the left of this point is not a valid criterion for the differentiation of organic from functional murmurs. Murmurs audible at the apex of the heart must be differentiated from the results of diffusion of sounds which are of greatest intensity at a point which implies no pathologic significance.

Summary

A group of 500 children between the ages of 2 and 12 years was subjected to a special cardiac examination. Of these, 234 (46.8%) were found to have functional cardiac murmurs and 137 (27.4%) were found to have extra cardiac sounds.

There was a considerable degree of association between the occurrence of these two types of adventitious sounds. Neither, however, was found to be correlated with the

degree of anemia present, the age, color, sex, state of nutrition, or the temperature of the subjects examined.

A strong association was found to exist between the quality of many functional cardiac murmurs and their point of maximal intensity over the precordium, those in the midprecordium being commonly of the vibratory type and those in the pulmonic region of the blowing variety.

The most valuable criteria for the differentiation of functional from organic heart murmurs in childhood are the acoustic quality and the point of maximal intensity of the murmur.

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SPANISH ABSTRACT

Suceso de Inocentes Sonidos Cardíacos Adventicios en la Niñez

Se sometieron quinientos niños entre las edades de 2 y 12 a un exámen cardíaco especial. De éstos, 234 (46.8%) tenían murmullos cardíacos funcionales y 137 (27.4%) tenían sonidos extra cardíacos.

Había un considerable grado de asociación entre el suceso de estos dos tipos de sonidos adventicios. Ninguno, sin embargo, se encontró que estaba en correlación con el grado de anemia presente, la edad, color, sexo, estado de nutrición, o la temperatura de los sujetos examinados.

Se encontró que existía una fuerte asociación entre la calidad de muchos murmullos cardíacos funcionales y su punto de máxima intensidad sobre la precordia, aquellos en la midprecordia eran comunmente de tipo vibratorio y aquellos en la región de los pulmónica de una variedad de soplido.

Los criterios más valiosos para la diferenciación de los murmullos funcionales de los cardíacos orgánicos en la niñez son la calidad acústica y el punto de intensidad máxima del murmullo.

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PSEUDOHYPOPARATHYROIDISM

Case Report

By M. G. PETERMAN, M.D., AND J. L. GARVEY, M.D.
Milwaukee

THIS case is presented because the circumstances provided an unusual opportunity to review and study a rare condition. The child concerned had been diagnosed as having a case of hypothyroidism and epilepsy and the parents had been advised to place her in an institution. The child was referred to the authors in a further effort to obtain relief or advice.

CASE HISTORY

A 12 yr. old girl was examined because of "incessant talking in a silly, immature fashion; excessive greed for food and salt; lethargy, fatigue, over-affection and clumsiness, awkwardness, inability to skate or ride a bicycle."

A year before admission she began to scream in her sleep once or twice every night. Six months later she began to scream during the day. The attacks of screaming occurred suddenly without warning. She abruptly stopped what she was doing, stared ahead and screamed in a loud, hoarse voice for several seconds. Immediately afterward, she was embarrassed and tried to withdraw from the scene. Treatment elsewhere with adequate doses of phenobarbital, tridione, benzedrine, thyroid and pituitary extract had been ineffective.

Report of a previous examination at a university clinic was "moderately plump girl with a round face and lethargic appearance. There was narrowing of the right palpebral fissure and mild ataxia of the lower extremities. The physical examination was otherwise unimportant. The IQ was 80."

Examination later at a hospital-clinic was reported as "revealing obesity and cretinism in spite of a basal metabolic rate of minus 6 and minus 7."

Mother and father are intelligent and the 4 siblings are normal and well-adjusted. There is no history of convulsive disorders or mental disease.

The mother had been ill during this pregnancy and at the 4th mo. had almost miscarried. Delivery and infancy of the patient were normal. She had always been hungry, had never lost her "infantile fatness," and had always had a hoarse voice and often a crowing inspiration. She weighed 3.6 kg. at birth, walked at 17 mos., and talked at 2 yrs. She had cramps in her feet early and walked on the outsides of the feet. She had complained of numbness and tingling in her extremities at 2 and 3 yrs. of age.

Patient was admitted to the Milwaukee Children's Hospital aged 12 yrs. Wt. was 45.8, ht. 147 cm. (−1 standard deviation). Round pudgy face with slightly yellow color of the skin and generalized myxedematous appearance (Fig. 1) were noted on examination. The face bore resemblance to that of a 12 yr. old girl reported by Albright et al.[1] Chvostek facial reflex was active as were the ulnar and peroneal reflexes. Trousseau test was negative. Voice was hoarse and coarse. Teeth were small and immature. Pharyngeal reflex was absent. Deep tendon reflexes were normal in the upper extremities but could be obtained only occasionally in the lower. Feet were in pes cavus position. There were small areas of calcification in the skin over both calves, both hips and the ulna side of the right wrist.

The seizures suggested some type of tetany and not epilepsy. They consisted of sudden loud outbursts of squealing and shouting without aura, without twitching or loss of equilibrium. Pupils were dilated, mouth held open and extremities tense. There was no loss of sphincter control. She had from 5 to 15 seizures during the day and night and was embarrassed and realized what had happened immediately after the seizure.

Serum calcium of 6.6 mg./100 cc. blood and phosphorus of 11 mg./100 cc. suggested the diagnosis of hypoparathyroidism. The inorganic phosphorus-excretion in the urine of 0.7 gm. (control 1.7 on same diet) in 24 hrs. gave further evidence of this.

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FIG. 1. J. C., 12 yrs. old. May 1948.

After 3 wks. of treatment phosporus excretion was 1.77 gm. and serum prosphorus was 6.5 mg./100 cc. Sugar tolerance test was normal (Table I). Sulkowitch calcium test of the urine had been negative throughout and to the date of the 2nd admission.

Lateral roentgenogram of the skull showed scattered areas of calcification in the basal nuclei and generalized osteoporosis of the skull (Figs. 2 and 3). These observations prompted a roentgenologic survey which showed generalized osteoporosis and demineralization of all the bones (Figs. 4 and 5).

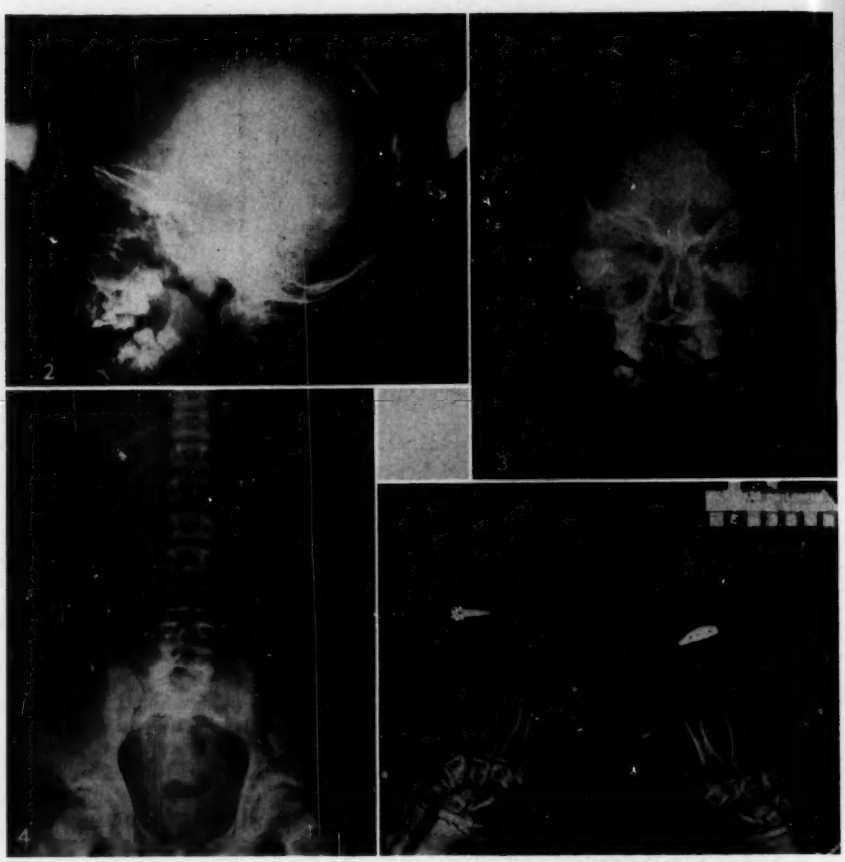
Dr. John P. Caffey, New York, reviewed the roentgenograms and made this report: "I see no changes which warrant a roentgen diagnosis of hyperparathyroidism. Characteristic changes in hypoparathyroidism have never been described in the skeleton as far as I know. Camp, of the Mayo Clinic, found calcifications in the basal nuclei of the brain in some of his patients. The calcification in the soft tissues in the left inguinal region is difficult to explain on the basis of either hyperparathyroidism or hypoparathyroidism. Usually in hyperparathyroidism the extraskeletal calcifications are found mostly in the kidneys. The changes in the skull are interesting but it is difficult to attach any special

TABLE I

BLOOD AND URINE CHEMISTRY

J.C.

Blood Serum	May 3	5	10	17	22	28	June 2, 1948
Calcium mg./100 cc. per cent	6.6	6.56	6.8	7.4	8.4	9.2	9.4
Phosphorus mg./100 cc. per cent	—	11.0	—	8.7	6.5	6.8	7.4
Phosphatase Bodansky u.	—	6.9	—	—	—	—	—
Chlorides mg./100 cc. per cent	—	—	479	—	—	—	—
T. protein per cent	—	6.1	—	—	—	—	—
NPN mg./100 cc per cent	—	—	—	—	—	33	—
May 11, 1948 Urine	Inorg. P. 0.7 gm. 24 hrs.						
Control (on same diet)	1.7 gm. 24 hrs.						
May 21, 1948 Urine	Inorg. P. 1.77 gm. 24 hrs.						
May 3 to June 6	Urine Sulkowitch negative.						



FIGS. 2-5. J. C., 12 yrs. old. May 1948.

clinical significance to them. The diploic space is widened in the frontal and parietal bones and the outer table is thin. The pituitary fossa appears to be unusually small in all films. Also, in all projections the mandible is absolutely and relatively enlarged and the small teeth are crowded together in the body of this bone. In practically all the films there are numerous patches of increased density which appear to be in the cerebrum but it is difficult to locate them accurately. It is interesting that they are not situated exclusively in the position of the basal nuclei where Camp found calcification in hypoparathyroidism. The roentgen findings are so vague and the interpretation so uncertain that I think they should be given little weight in final diagnostic evaluation. The most significant changes are probably the intracerebral calcifications which support in a secondary fashion the diagnosis of hypoparathyroidism."

Dr. John D. Camp, Rochester, Minn., one of the pioneers in the roentgenologic study of this disease,[2] also reviewed the roentgenograms of this patient and made the following comments: "The osteoporosis that is present in the various films is not in keeping with any case of hypoparathyroidism that I have seen. There are several minimal shadows of calcification in the basal ganglia of the brain which I have observed frequently in patients with spontaneous hypoparathyroidism. The urogram would seem to indicate pathology in one kidney. There also are calcium deposits about the right hip joint, in some of the soft tissues of each lower leg and about the tip of the ulna of one forearm.

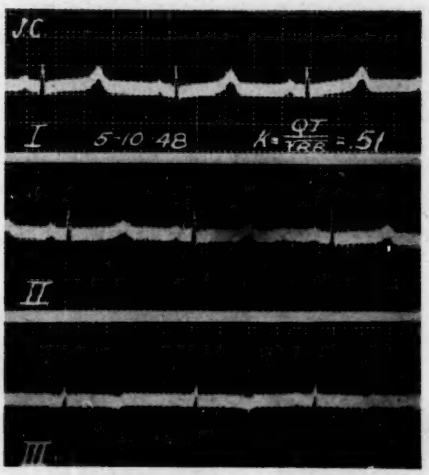


FIG. 6. 1st ECG with prolonged Q T interval .51.

These are not found in hypoparathyroidism. The films of the skull, as I stated previously, reveal the presence of calcification distributed rather symmetrically in the cerebral basal ganglia. There are also several areas of calcification in the cortex on either side. These are the changes that are commonly observed in roentgenograms of the skull in patients with spontaneous hypoparathyroidism. I am still

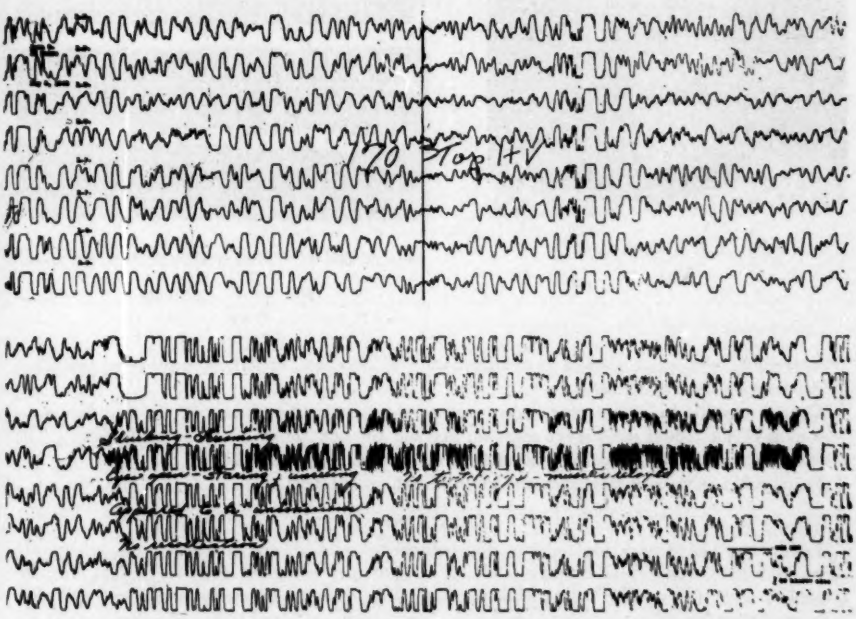


FIG. 7. Upper section: EEG taken before and during tetanic episodes. Lower section: EEG taken after hyperventilation.

unable to reconcile the osteoporosis with this diagnosis. I do not recall having seen it in any of our cases. Apparently the question of renal pathology has been excluded so the osteoporosis cannot be explained on that basis."

ECG revealed a marked increase in the $Q = T$ interval. $K = \frac{QT}{\sqrt{RR}} = .51$ (upper limits of normal, .4 to .42). (See Fig. 6.)

EEG (Grass apparatus in the office of M. G. P.) taken before and during tetanic episodes and after hyperventilation were not typical of the dysrhythmia of the convulsive state (Fig. 7).

Binet-Simon mental test gave an intelligence quotient of 79.

Rorschach test was reported as follows: "There is much in the test to indicate an organic brain disturbance of an epileptic or convulsive type."

FIG. 8. J. C. Sept. 1948.

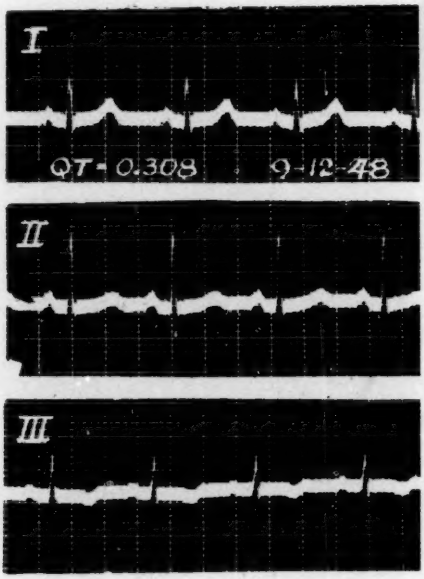


FIG. 9. 2nd ECG after treatment. Sept. 12, 1948. $K = \frac{QT}{\sqrt{RR}} = 0.308.$

Intravenous pyelogram showed normal-appearing kidneys and ureters. Mosenthal concentration kidney function test was normal.

Dental consultation with roentgenograms revealed a "congenital absence of the 2nd bicuspids. The roots of the central incisors are short for age and size and the apices are not well formed. The bone below apices of the 2nd deciduous molars is thin and not highly calcified."

Examination of the eye revealed no abnormalities and no cataracts.

TREATMENT

Patient was placed on a high-calcium, low-phosphorus, acid-ash diet which kept the urinary pH down to 5 to 6. Parathyroid extract (Lilly), .1 cc. (10 u.), was given daily for 2 days, then increased to .2 cc. (20 u.) for 2 days without effect on the tetany or on the serum calcium. Dihydrotachysterol (hytakerol®) 1 cc. (1.25 mg.) was given 3 times daily and increased 5 days later to 1.5 cc. 3 times daily. Calcium diphosphate (Squibb) .25 gm. with viosterol 330 u. was given 3 times daily. Ammonium chloride (Lilly's enseals) .25 gm. was given 3 times daily after 14 days.

TABLE II

BLOOD AND URINE CHEMISTRY

J.C.					1948					
Blood Serum		Sept. 8	14	21	28	29	Oct. 6	28	Nov. 8	Dec. 11
Calcium mg./100 cc. per cent		10.0	10.2	10.0	9.9	9.7	9.4	9.6	9.66	9.2
Phosphorus mg./100 cc. per cent		5.5	5.3	5.9	5.75	6.65	6.2	6.2	5.65	5.7
Phosphatase Bodansky u.		4.5	6.2	—	—	—	—	—	—	—
T. protein per cent		6.5	6.1	—	—	—	—	—	—	—
NPN mg./100 cc. per cent		22	29.8	—	—	—	—	—	—	—
Urine Sulkowitch	9/ 8/48 to 9/25/48	Normal calcium concentration.								
	10/ 4/48 to 10/ 9/48	No precipitate.								
	10/11/48 to 11/ 9/48	Normal calcium concentration.								
	11/10/48 to 11/13/48	No precipitate.								
	11/15/48 to 11/18/48	Normal calcium concentration.								
Sept. 27, 1948	Urine Phosphorus	0.91 gm. 24 hrs.								
	Control (on same diet)	1.1 gm. 24 hrs.								

Patient was discharged after 25 days. There was a gradual but progressive decrease in seizures to none for 3 days, then 5 a day.

Serum calcium was 7.9 mg./100 cc. and phosphorus was 6.7 mg./100 cc. 1 mo. later.

Patient was readmitted to the Milwaukee Children's Hospital 4 mos. later for further study (see Figs. 8 and 9). Her tetanic episodes had diminished considerably in frequency and in severity. There were still occasional episodes, however, sometimes 4 a day. Her voice was much softer, mouth much less contracted and facial expression better (Fig. 8). Chvostek and peroneal reflexes were negative; ulnar reflex was normal. Urine contained a normal amount of calcium but the phosphorus excretion in 24 hrs. had dropped to 0.19 gm.

Serum calcium was 10 mg./100 cc., phosphorus 5.5 mg./100 cc. blood (Table II).

Tetanic episodes continued 1 to 8 in 24 hrs., sometimes with 1 to 2 days of complete freedom. The character of the seizures varied with the quantity of calcium in the urine. They occasionally became major convulsions with generalized twitching but with no aura and no loss of voluntary control.

TABLE III

RESULTS OF THE ELLSWORTH-HOWARD TEST

J.C.	Sept. 28, 1948	
	Urine Phosphorus mg./100 cc.	Serum Phosphorus mg./100 cc.
Fasting	—	5.75
1st hr.	12.5	—
2nd hr.	6.1	—
3rd hr.	15.3	—
30 U. Parathyroid Extract injected intravenously . . . Postinjection:		
1st hr.	12.8	—
2nd hr.	29.4	—
3rd hr.	10.8	—
4th hr.	10.0	—
Fasting—24 hrs. later		6.65

Amphetamine sulfate (benzedrine), glutamic acid, phenurone (phenacetylurea),* parathyroid extract, dihydrotachysterol and a ketogenic diet were used as trial therapeutic agents during this period.

Ellsworth-Howard test of phosphorus excretion in the urine showed a response typical of pseudohypoparathyroidism (Table III).[3]

Patient was readmitted to Milwaukee Children's Hospital again later. Wt. was 53.5 kg. There had been no further seizures. She had made good progress in school. Attention span was increased and mentality much improved. Voice was normal. During this entire period the Sulkowitch test on the urine had been negative. She still had the round full face. Chvostek facial reflex, ulnar and peroneal reflexes were still present.

Roentgenograms of the bones showed much increase in calcium deposits. Laboratory findings were NPN 36 mg./100 cc., serum Ca 8.6 mg./100 cc., serum P 8.2 and 8.5, phosphatase 8.9, serum protein 6 gm./100 cc., urine Sulkowitch negative. Ellsworth-Howard test is shown in Table IV.

TABLE IV

RESULTS OF THE ELLSWORTH-HOWARD TEST

J.C.	August 8, 1949
Phosphorus:	7 a.m.—Specimen unmarked and run as routine
	8 a.m.—Unable to void
Parathyroid	9 a.m.—46.8 mg./51 cc. urine or
1 cc. I.V.	90.0 mg./100 cc. urine
	10 a.m.—Unable to void
	11 a.m.—39.5 mg./45 cc. urine or
	90.0 mg./100 cc. urine
	12 a.m.—17.0 mg./20 cc. urine or
	85.0 mg./100 cc. urine
	1 p.m.—20.6 mg./206 cc. urine or
	10.0 mg./100 cc. urine
Urinary Sulkowitch—	8/9—neg.
	8/10—neg.
	8/11—neg.

COMMENT

Albright et al.[1] have reported three cases of pseudohypoparathyroidism. The case reported here is almost identical with Albright's Case 2. Photographs of the faces of the two patients (both 12 year old girls) are almost indistinguishable and are short, rather thick-set and round. The index fingers in our patient, however, were not longer than the middle fingers. Both patients had low calcium and high phosphorus values in the blood serum and low phosphorus excretion in the urine. Neither case responded to parathyroid extract and both required large doses of dihydrotachysterol to control the tetany.

The most striking difference between the cases and the most unusual feature of our case is the demineralization or osteoporosis of the bones. This is a characteristic of hyperparathyroidism.

The primary action of the parathyroid hormone is to diminish the reabsorption of phosphate in the renal tubules. Parathyroid extract causes decalcification of bone. Dihydrotachysterol also produces demineralization of bone[4–6] and has done so in this case.

Another feature is the failure of the patient to respond to calcium therapy alone and the change in the type of seizures.

This finding substantiates Albright's suggestion that "the disturbance was not a lack

* Provided by Abbott Laboratories, North Chicago, Ill.

of the hormone but a resistance to it." In our case the demineralization has progressed since treatment was started with dihydrotachysterol.

Attention is also directed to the fact that the history in our case suggested hypoparathyroidism from early infancy. Two photographs of the child show a physical appearance typical of pseudohypoparathyroidism and attention is called to Albright's photograph so that similar cases may be recognized. The blood chemistry and urinary findings and ECG confirmed the diagnosis. They were useful in evaluating the results of treatment. The EEG was extremely useful in helping to exclude the diagnosis of idiopathic epilepsy.

It is believed that idiopathic epilepsy is excluded also because this patient failed to respond to the many anticonvulsants which had been given. An apparent response to phenacetylurea at the end of the treatment was not convincing because the drug was not effective in much larger doses before the calcium metabolism was regulated.

The history and physical examination made possible the diagnosis of this rare and unusual case.

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Spanish Abstract

Seudohipoparatiroidismi; Relato de un Caso

Se presenta un caso típico de seudohipoparatiroidismo en una niña de 12 años de edad. El caso de por sí fué típico de hipoparatiroidismo. El exámen médico reveló una cara llena, redonda característica en una muchacha baja y gorda con reflejos peroneales cubitales, faciales positivos. El calcio del suero estaba bajo, el fósforo del suero alto y la excreción fósfora urinaria estaba baja.

La inyección de extracto paratiroideo intravenosamente produjo un aumento de fósforo en la excreción urinaria.

Una característica estraña de este caso fué la desmineralización de todos los huesos.

411 East Mason Street

SKIN REACTIONS TO TOXOPLASMIC ANTIGEN IN PEOPLE OF DIFFERENT AGES WITHOUT KNOWN HISTORY OF INFECTION

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FOLLOWING the observation reported by Warren and Russ,[1] that an extract of toxoplasma-infected chorioallantoic membranes contains a substance which elicited a delayed, cutaneous inflammatory reaction in an individual possessing antibodies for Toxoplasma, studies were carried out in this laboratory to determine the specificity and significance of this reaction. Preliminary observations by one of the authors (A. B. S.) indicated that in people whose serum contained toxoplasmic antibodies there appeared 30 to 48 hours after intracutaneous injection a distinct, severe inflammatory reaction at the sites inoculated with the extract of toxoplasma-infected chorioallantoic membranes but not at the sites inoculated with the extract of normal chorioallantoic membranes. No such reaction was found in individuals whose serum contained no toxoplasmic antibodies. Frenkel[2] recently reported on "dermal hypersensitivity to toxoplasma antigens (toxoplasmins)" derived not only from infected chorioallantoic membranes but also from sedimented peritoneal exudates containing large numbers of Toxoplasma, and recommended the "toxoplasmin skin test" for the diagnosis of toxoplasmosis. A comparative study of recently developed serologic methods and the skin test, to be published elsewhere,[3] indicated that while the skin test had little or no diagnostic value, it might, nevertheless, be useful for population survey purposes as an index to the probable incidence of inapparent infection with toxoplasma. The present communication deals with the results of such a survey of 142 people, aged 3 months to 81 years, who at the time of the study happened to be residents of the Cincinnati area. Data concerned with the relationship between the skin sensitivity and the presence of toxoplasmic antibodies in the serum of some of these people are also presented.

METHOD OF STUDY

The toxoplasmic skin test antigen and the control antigen derived from the chorioallantoic membranes of uninoculated 16 day old embryonated chicken eggs were prepared by Warren and Russ[1] and supplied by Dr. Joel Warren. The Toxoplasma were killed by freezing and thawing and then removed from the test antigen by centrifugation. There is no evidence that the freezing and thawing contribute anything to the antigen. Merthiolate in a final concentration of 1:10,000 was present in both the toxoplasmic and control antigens, but both preparations were checked for sterility by cultures and inoculation of mice and guinea pigs. The original 20% or 10% centrifuged extracts (regarded as the 1:5 or 1:10 dilutions for purposes of further dilution) were either stored at —20° C. or in a "dry ice" chest, or after lyophilization in an ordinary refrigerator; however, the potency is retained for at least 2 to 3 mos. even when the material is stored in the fluid state in an ordinary refrigerator. The flocculent precipitate, appearing when the frozen material is thawed, was removed by light centrifugation and 1:100, 1:1,000 and 1:10,000 dilutions in sterile, 0.85% solution of NaCl were pre-

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pared prior to use. Preliminary tests on individuals, without history of infection, but whose serum neutralized Toxoplasma in the rabbit test[4] and yielded titers of 1:16 to 1:64 in the dye test,[8] indicated that while the 1:10,000 dilution frequently gave minimum positive reactions, the most striking lesions were produced by the 1:100 and 1:1,000 dilutions. The toxoplasmic skin test antigen also contained the specific complement-fixing antigen; 0.25 cc. of the 10% extract (or 1:10 dilution) contained 4 units of complement-fixing antigen when tested against 16 u. of antibody in a test employing 2 exact u. of complement.[6]

The following procedure was used in skin testing: the flexor surfaces of both forearms were cleansed with acetone-alcohol, permitted to dry and then 0.1 cc. of the test solutions were injected intracutaneously. Toxoplasmic and control antigens were placed in separate forearms, the more dilute solutions being injected at least 6 cm. distal to the more concentrated. Readings were made at approximately 24 and 48 hrs., although it was apparent that in some individuals 30 to 40 hrs. would have been the optimum time for recording the definitive result. One hundred forty-two residents of the Cincinnati area ranging in age from 3 mos. to 81 yrs. were included in this survey. Twenty-three of these people were members of the medical, nursing and laboratory staffs and 119 were selected at random from patients at the Cincinnati General and Children's Hospitals. Neither patients with known congenital toxoplasmosis nor their mothers were included in this group. Selection for inclusion in this survey was based chiefly on age and absence of fever. A history of allergic manifestations following the eating of eggs would have excluded any individual from this survey, but no such person was encountered.

Results

Within a few minutes after injection of either the toxoplasmic or the control antigens, some individuals exhibited a distinct zone of erythema at the inoculated sites varying in size from 15 x 15 mm. to 40 x 40 mm., unaccompanied by edema, pseudopods or itching. However, this immediate reaction disappeared within about an hour and bore no relationship to what happened subsequently. Between 2 to 6 hrs., there then appeared an erythematous reaction measuring 10 x 10 mm. to 20 x 20 mm. at all inoculated sites, but this occurred only in a small proportion of individuals and usually disappeared within 30 hrs. In only 1 person in the entire group did this erythematous reaction persist at all sites for 48 hrs. The specific toxoplasmic reaction was characterized not only by erythema, but also by edema, induration, tenderness and itching. The reaction reached its maximum at 30 to 36 hrs. and with few exceptions was still at its maximum between 48 and 72 hrs. A few individuals were encountered in whom the erythema (but not local tenderness or itching) disappeared at 48 hrs., but even in these it was possible to bring back the focal erythema by temporary passive congestion. The reactions were recorded at 48 hrs. and only those with a minimum lesion of 10 x 10 mm. occurring only at the sites inoculated with toxoplasmic antigen were regarded as positive. At the sites inoculated with the 1:100 dilution of toxoplasma antigen, the usual reactions ranged from 30 x 20 mm. to

TABLE I

Incidence and Age Distribution of Positive Skin Reactions to Toxoplasmic Antigen Among 142 Residents of Cincinnati Area without Known History of Infection

Age Group Yrs.	Males		Females		Males and Females		
	Tested No.	Positive No.	Tested No.	Positive No.	Tested No.	Positive	
						No.	Per Cent
0–4	12	0	8	0	20	0	0
5–9	12	0	8	1	20	1	5
10–19	8	0	14	3	22	3	14
20–29	14	2	6	2	20	4	20
30–39	13	7	7	3	20	10	50
40–49	15	9	5	4	20	13	65
50–81	17	10	3	3	20	13	65
All Ages	91	28	51	16	142	44	31

60 x 50 mm., while the reactions at the sites inoculated with the 1:1000 dilution were usually about half this size. All reactions disappeared within 4 to 7 days and none ulcerated. A few people complained of headache and malaise at the peak of the local reaction, 30 to 48 hrs. after inoculation. The 1st 98 persons to be tested in this survey received both the 1:100 and 1:1000 dilutions and among the 28 who developed a specific positive reaction to the 1:100 dilution, 24 (86%) also had positive reactions at the 1:1,000 sites. Since no correlation was found between the severity and extent of the skin reaction and titer of toxoplasmic antibodies in the serum as measured by the dye test, the remaining people in this survey received only the 1:100 dilution because the reaction to this concentration of antigen was more definitive.

The incidence of specific positive skin reactions among individuals of different ages, summarized in Table I, was found to be 5% or less among those under 10 yrs. of age, 14 to 20% between 10 and 29, 50% in the 30 to 39 yr. old group and 65% among the 40 people tested in the 40 to 81 yr. age group. The youngest individual in this group to give a positive reaction was an 8 yr. old girl. This unexpectedly high incidence of positive skin reactions with toxoplasmic antigen among individuals over 30 yrs. of age without any history of recognized infection with this protozoon parasite made it necessary to determine somewhat more extensively the relationship btween skin reactivity and antibodies against Toxoplasma. Serum on a number of these individuals was available before inoculation with toxoplasmic antigen and others were bled within 2 to 3 days after inoculation. All sera were tested for toxoplasmic antibodies by the dye test,[5] recently developed in this laboratory and found to yield the most reliable quantitative data. Some of them were also tested for neutralizing antibodies in rabbits[4] and mice and for complement-fixing antibodies[6] using the same toxoplasmic material employed for skin testing as antigen. The relationship between the results of the skin tests in individuals of different ages and of the dye tests for toxoplasmic antibodies in their serum is shown in Table II. Among the 21 individuals of this group with positive skin tests all had toxoplasmic antibodies in titers ranging from 1:4 to 1:1,024, 2 (9.5%) had titers of 1:4, 13 (62%) had titers of 1:16, 4 (19%) had titers of 1:64 and there was 1 each (5%) with titers of 1:256 and 1:1,024, respectively. Studies on experimental animals and human beings with proved toxoplasmic infection have shown[2,5] that titers of 1:256 or 1,024 or higher are found shortly after or within at most 5 yrs. after infection. Similar tests on various patients suspected of having been infected with Toxoplasma, indicated that a positive toxoplasmic skin test was invariably associated with toxoplasmic antibodies (dye test method) in the person's serum, although the reverse was not true, i.e., a negative skin test did not necessarily mean absence of such antibody. It is of interest, therefore, that among 18 such individuals without history suggestive of toxoplasmic infection whose serum was tested, there were 7 (39%) with antibody demonstrable by the dye test—3 with titers of 1:16 and 1 with a titer of 1:256. It should be noted that 5 of these 7 positive sera (titers—undil., 4, 16, 16, 256) were obtained just before the skin test was performed and the positive results cannot be attributed to a

TABLE II

CORRELATION BETWEEN SKIN REACTIONS TO TOXOPLASMIC ANTIGEN AND SERUM ANTIBODIES FOR TOXOPLASMA AS DETERMINED BY DYE TEST

Age Group Yrs.	Skin Tests Positive		Skin Tests Negative	
	Toxoplasmic Antibody		Toxoplasmic Antibody	
	No. Positive/ No. Tested	Titers of Positive Sera	No. Positive/ No. Tested	Titers of Positive Sera
0–19	3/3	16, 16, 16	0/3	—
20–29	3/3	4, 16, 16	1/5	Undiluted
30–39	5/5	4, 16, 64, 64, 256	1/3	256
40–49	4/4	16, 16, 16, 1024	1/2	4
50–59	5/5	16, 16, 16, 16, 64	3/3	16, 16, 16
60–81	1/1	64	1/2	4
All Ages	21/21	100% Positive	7/18	39% positive

possible booster effect of the inoculated toxoplasmic antigen. It is perhaps also noteworthy that these 5 individuals were employees of the public park system whose duties included cleaning out pigeon manure. Several months before these 5 people were tested, Toxoplasma was recovered from the viscera of 1 trapped pigeon whose serum also had antibodies in a titer of 1:1024 (dye test), while toxoplasmic antibodies (dye test titer of 1:64) were demonstrated in the serum of 2 of 20 additional pigeons.[7]

Rabbit tests for neutralizing antibodies were carried out on the sera of 28 people without a history suggestive of toxoplasmic infection—14 with positive skin tests and 14 with negative skin tests. The results, shown in Table III, are comparable to those obtained with the dye test which is more sensitive than the rabbit test. In our experience, sera with a dye test titer of 1:4 or less give negative rabbit tests and sera with dye test titers of 1:16 may occasionally give an equivocal result in the rabbit test. The complement fixation tests on 19 individuals, shown in Table III, indicate that there is no correlation between the results of the skin test and the complement-fixing antibodies. The

TABLE III

CORRELATION BETWEEN SKIN REACTIONS TO TOXOPLASMIC ANTIGEN AND SERUM ANTIBODIES FOR TOXOPLASMA AS DETERMINED BY NEUTRALIZATION TEST IN RABBITS OR BY COMPLEMENT FIXATION

Result of Skin Test	Toxoplasmic Antibodies in Serum Determined by			
	Neutralization Test in Rabbits		Complement Fixation	
	No. Tested	Result	No. Tested	Result—Titer
Positive	14	12 positive 1 equivocal 1 negative	10	1:2 3 positive—1:2 1:32
Negative	14	1 positive 1 equivocal 11 negative	9	1 positive—1:16

1 individual in the skin test positive group whose serum gave a complement fixation titer of 1:32 and had a dye test titer of 1:1,024 gave only a minimum positive skin reaction with the 1:100 dilution of antigen and none at all with the 1:1,000 dilution. In the skin test negative group, the 1 individual whose serum yielded a positive complement fixation test did so in a titer of 1:16 and the dye test titer (which is a measure of the neutralizing antibody) was 1:256. Other studies in this laboratory[6] have indicated that while the complement-fixing antibody may persist in human beings for several years after inapparent infection (mothers who gave birth to children with congenital toxoplasmosis), it ultimately disappears while the neutralizing antibodies persist although in lower titer. It is, therefore, evident that although a positive skin test indicates presence of toxoplasmic neutralizing antibody, it is no index to activity of toxoplasmic infection, and a negative skin test does not mean absence of toxoplasmic antibodies. It is, nevertheless, possible by means of the skin test to obtain a crude indication of the incidence of toxoplasmic antibodies among certain population groups. However, our data indicate that the actual incidence of antibodies, particularly among the older age groups, may be considerably higher than the results of a skin test survey might suggest. Since according to the present skin test survey data only 5% of the children (1 of 20) in the 5 to 9 yr. age group were positive, it was of interest to carry out the dye test for toxoplasmic antibodies on the sera of 10 children from the Cincinnati area aged 5 to 6, which we happened to have in the laboratory. Only 1 of the 10 was positive and that was the serum of the 6 yr. old child which had a titer of 1:16.

An additional observation, which is consistent with the frequent occurrence of toxoplasmic antibodies among adults, concerns the finding of a dye test titer of 1:256 in a sample of human gamma globulin (immune serum globulin [human] control No. 82-3, Squibb). Information supplied by the manufacturer indicated that this globulin concentrate was prepared from a pool of 6,017 l. of Red

Cross plasma, which was derived from an estimated 20,000 to 150,000 adults in various parts of the country. Since this preparation was said to represent a 15 to 20 fold concentration of the gamma globulin in the original plasma, it is apparent that the titer of toxoplasmic antibody in the original plasma was probably in the range of 1:16, assuming that all the antibody went into the gamma globulin fraction and that there was no other loss during the process of purification. It is clear that this result might be expected if the incidence of toxoplasmic antibodies among the adult population was of an order of magnitude similar to that obtaining in the Cincinnati area, as shown in Tables I and II.

Since a study of the nature of the complement-fixing antigen revealed that it is a soluble substance existing apart from the intact Toxoplasma in the peritoneal exudate of mice,[6] it was of interest to determine (a) whether or not the skin test antigen could also be found in such exudates deprived

TABLE IV

REACTION OF HUMAN SUBJECTS TO INJECTIONS OF MOUSE PERITONEAL EXUDATE FREED OF TOXOPLASMA BY CENTRIFUGATION

Subject	Time After Injection-Hrs.	Dilution of Centrifuged Mouse Peritoneal Exudate		Remarks
		1:160	1:1600	
A.	8	15×10 mm.—swollen, red	0	
	24	28×26 mm.— " "	15×10 mm.—swollen, red	
	32	40×40 mm.— " "	25×18 mm.— " "	Lesions tender and itching; headache, flushed, no fever.
	48	55×55 mm.— " "	30×25 mm.— " "	Tenderness gone. Itching persists. Headache gone.
H.	8	10×10 mm.—red	5× 5 mm.—red	
	24	28×28 mm.—swollen, red	18×13 mm.—swollen, red	Lesions tender and itching.
	36	40×30 mm.— " "	30×25 mm.— " "	Generalized malaise, no fever.
	48	65×55 mm.— " "	45×40 mm.— " "	Malaise disappeared at about 54 hrs. after inoculation

of Toxoplasma by centrifugation and (b) whether or not its concentration would be proportional to that of the complement-fixing antigen. The exudate and saline washings of the peritoneal cavities of 30 mice (4 days after intra-abdominal injection of Toxoplasma), totalling 60 cc., was first centrifuged at about 2,000 rpm for 20 min. The supernatant liquid was further centrifuged at 13,000 rpm (Sorvall Swedish Angle Centrifuge—SS1) for 2 one hour periods in the cold room in an unsuccessful attempt to diminish its anticomplementary titer. However, this preparation, which was not anticomplementary in a dilution of 1:16, fixed 2 exact u. of complement completely in a dilution of 1:64 in the presence of toxoplasmic antiserum.[6] The material was sterile and free of Toxoplasma according to results of animal inoculation. Since the 10% extract of infected chorioallantoic membranes (i.e., the 1:10 dilution) contained 4 u. of complement-fixing antigen under the same conditions, the centrifuged peritoneal exudate was diluted 1:16 with 0.85% solution of NaCl to render it comparable to the toxoplasmic egg antigen. Further 10 fold dilutions yielding 1:160 and 1:1,600 dilutions of the mouse peritoneal exudate (comparable to the 1:100 and 1:1,000 dilutions of the egg antigen) were used on 2 human beings who, 1 yr. ago, gave strong positive reactions with both the 1:100 and 1:1,000 dilutions of the toxoplasmic egg antigen and whose sera both had dye test titers of 1:64. The positive reactions (Table IV) were of the same severity and occurred at the same time as those which were observed earlier following the inoculation of the toxoplasmic egg antigen. Thus, it would appear that the toxoplasmic skin test antigen is a soluble substance present in abundance in infected exudate and apparently also proportional to the concentration of the complement-fixing antigen.

Discussion

The high incidence of positive skin reactions to toxoplasmic antigen and the apparently still higher incidence of toxoplasmic antibodies among "normal" adults in the Cincinnati area revealed in the present survey naturally raises the question whether this is all due to inapparent or unrecognized infection with Toxoplasma. Thus far no infectious agent is known to possess a common antigen with Toxoplasma or to be capable of giving rise to antibodies for it. While this possibility remains, it is not improbable that Toxoplasma are frequently transmitted to human beings from its large reservoir in domestic animals, rats, pigeons, etc., although it is curious that the incidence of antibodies (and presumably infection) should rise so sharply after the 20th year of life. Whether the Cincinnati area is peculiar either in the high incidence or in the age distribution cannot be determined at this time because there are no comparable data. Sabin[4] estimated that 10% of the population in the Cincinnati area (not analyzed according to age) had toxoplasmic antibodies as determined by the rabbit test. Callahan,[8] using what might be an undesirable modification of the rabbit test (his inoculum being 0.02 cc. instead of 0.2 cc.), reported that only 2.7% were positive among 74 people, aged 18 to 28 yrs., residing in the St. Louis area. Heidelman[9] reported that 10% of 58 "normal" persons of unspecified age in the Baltimore area gave positive or equivocal rabbit tests for toxoplasmic antibody. Frenkel,[2] who may have used toxoplasmic antigen in greater dilution than that employed in the present study, reported that 10% of 50 "normal" people aged 20 to 35 years and 28% of 50 hospital patients, aged 50 to 83 years, in the San Francisco area gave positive skin reactions. It is apparent that the data reported in the present communication need to be enlarged both numerically and geographically for a proper evaluation of the role of Toxoplasma in human disease.

Summary

One hundred forty-two residents of the Cincinnati area ranging in age from 3 months to 81 years were surveyed for their reaction to the intracutaneous injection of toxoplasmic antigen prepared from infected chorioallantoic membranes of chicken eggs. The skin test antigen is also present in abundance in mouse peritoneal exudate freed of Toxoplasma by centrifugation and its concentration appears to be proportional to that of the complement-fixing antigen. The positive reactions, consisting of red, indurated, swollen, tender and itching lesions ranging in size from 60 x 50 mm. to 10 x 10 mm. (the latter being relatively rare), reach their maximum in 30 to 48 hours. The incidence of positive reactions among at least 20 individuals in each age group listed was as follows: 0 to 4 years—0; 5 to 9 years—5%; 10 to 19 years—14%; 20 to 29 years—20%; 30 to 39 years—50%; 40 to 49 years—65%; 50 to 81 years—65%. A positive skin test was invariably associated with demonstrable toxoplasmic antibody in the serum. Toxoplasmic antibody in varying titer was also found in the serum of 7 of 18 persons (39%) with negative skin tests. Further evidence in favor of the high incidence of toxoplasmic antibody among the "normal" adult population was obtained when a 15 to 20 fold concentrated, commercial preparation of gamma globulin prepared from the plasma of more than 20,000 American adults was found to contain toxoplasmic antibody in a titer of 1:256 as determined by the dye test. Since no agent having an antigen in common with Toxoplasma and capable of giving rise to antibodies for this protozoon parasite has been found thus far, one must consider the possibility that inapparent infection with Toxo-

plasma may be widespread, although it is rather curious that the incidence of antibodies (and presumably infection) should rise so sharply after the 20th year of life. The toxoplasmic skin test is not useful for diagnosis because a strongly positive test bears no relationship to titer of antibody and a negative test is encountered too often in the presence of antibody.

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Spanish Abstract

Reacciones de la Piel al Antígeno Toxoplásmico en Personas de Diferentes Edades Sin Historia de Infección Conocida

Se vigilaron 142 residentes de Cincinnati de 3 meses a 81 años de edad para ver la reacción al antígeno toxoplásmico intracutáneo preparado de membranas corioalantoicas infectadas de huevos de gallina. El antígeno de análisis de la piel está también presente en el exudado peritoneal del ratón desembarazado de Toxoplasma mediante centrifugación y su concentración parece ser proporcional a la del antígeno de fijación de complemento. Reacciones positivas, consistiendo en lesiones rojas, endurecidas, inflamadas, sensibles y con picazón en tamaño de 60 x 50 mm. a 10 x 10 mm. (el último es relativamente raro), alcanzan su máximo en 30 a 48 horas. La incidencia de reacciones positivas entre por lo menos 20 individuos de cada grupo de edad apuntado fué 0-4 años—0; 5-10 años—5-10 años—5%; 10-19 años—14%; 20-29 años—20%; 30-39 años—50% 40-49 años—65%; 50-81 años—65%. Un análisis de piel positivo fué invariablemente asociado con anticuerpo toxoplásmico demonstrable en el suero. También se encontró el anticuerpo toxoplásmico en títulos variantes en el suero de 7 de 18 personas (39%) con análisis de piel negativo. St obtuvo más prueba a favor de la alta incidencia de anticuerpo toxoplásmico entre la población adulta "normal" cuando se descubrió que una preparación comercial concentrada de 15 a 20 veces de globulina de gama preparada de la plasma de más de 20,000 adultos americanos contenía anticuerpo toxoplásmico en un título de 1:256 determinado por el análisis de tinte. No se ha encontrado hasta ahora ningún agente que tenga un antígeno en común con Toxoplasma y capaz de dar origen a anticuerpos para este parásito protozoo, hay que considerar la posibilidad de que una infección invisible con Toxoplasma puede extenderse a pesar de que es más bien curioso que la incidencia de anticuerpos (e indudablemente infección) suba bruscamente después del vigesimo año de vida. El análisis de la piel toxoplástica no sirve para diagnosis porque en un ensayo fuertemente positivo no tiene relación con el titulo de anticuerpo y un ensayo negativo se encuentra muy amenudo en la presencia de anticurpo.

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OBSERVATIONS OF TOTAL SERUM BASE IN CHILDREN AND YOUNG ADULTS BY A CONDUCTIVITY METHOD

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DETERMINATION of total serum base has not been used extensively in clinical medicine because of the technical difficulty of the available methods.[1-4] A simple and inexpensive procedure has been presented by Sunderman.[5,6] The purpose of this study was to determine normal values for total serum base in children as measured by the conductivity method.

PROCEDURE

The method and necessary equipment was described by Sunderman.[5] Blood is drawn into clean glassware and centrifuged. Serum which has been used for pH determinations may be utilized. About 0.75 cc. of serum is drawn into the conductivity cell and the resistance is measured with the cell in a water bath which is about 25° C. With the cell constant which is known, the observed resistance of the serum and the total serum protein, the total base is read from a nomogram which is supplied with the instrument.* Corrections for temperature changes are made as described by Sunderman.[6] Certain technical difficulties were encountered which were not emphasized by Sunderman. Precipitation

TABLE I

Serum Total Base mEq./l.	mM Na Added per 0.5 cc. as NaCl	Calculated Total Base mEq./l.	Experimentally Obtained Total Base mEq./l.	% Error
149.0	0.5 cc H_2O No NaCl	99.3	110.8	11.58
149.0	0.007	104.0	113.6	9.23
149.0	0.015	109.3	119.0	7.97
149.0	0.031	120.0	127.0	5.83
149.0	0.046	130.0	134.0	3.07
149.0	0.062	140.6	143.0	1.77
149.0	0.077	150.6	154.0	2.25

of serum protein in the conductivity cell could be prevented only if exceptional care was taken in cleaning the cell after each determination. Serum proteins were determined by the method of Phillips and Van Slyke.[7] The errors in this method were recognized and frequent checks of the serum protein level were made by the micro Kjeldahl method. All protein values below 5.0 gm./100 cc. were checked by the micro Kjeldahl method. If there is any question of hypoproteinemia the protein should be determined by the Kjeldahl method since the error in the determination is considerably greater when the total serum protein is below 5.0 gm./100 cc.

The accuracy of the Sunderman method was checked in 5 ways. 1. Known amounts of sodium chloride were added to serum. The observed values were compared with the calculated values and found to check closely in dilutions approaching that of serum. These figures are shown in Table I.

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TABLE II

Serum Total Base mEq./l.	Total Amount of Sugar (Serum Addition) mg. %	Resultant Total Base Reading mEq./l.	H_2O Correction of Reading mEq./l.	Decrease Due to Sugar mEq./l.	Corrected Total Base mEq./l.
148.0	53.0	107.2	40.8	—	—
148.0	133.3	106.2	40.8	1.0	147
148.0	220.0	104.9	40.8	2.3	145.7
148.0	303.3	103.3	40.8	3.9	144.1
148.0	386.6	103.0	40.8	4.2	143.8
148.0	553.3	102.2	40.8	5.0	143.0
148.0	720.0	101.9	40.8	5.3	142.7
148.0	1053.3	101.0	40.8	6.2	141.8

When the concentration of total base was lower than that of normal serum, the observed values for total base by the conductivity method were 5.8 to 11.5% higher than the calculated values. This difference in conductivity method may be accounted for by a difference in ionic activity in the lower dilutions. 2. Sugar was added to serum in varying dilutions to find out the effect of the addition of sugar on conductance. These results are listed in Table II. The addition of sugar did not produce an appreciable error in the total base determination unless the concentration was high. The changes in column 3 of Table II are due to fluid addition and not to changes in sugar concentration. 3. Multiple determinations were made on 3 individuals who were well. These figures are listed in Table III. J. E. had 12 determinations on consecutive days. W. M. K. had daily determinations for 3 periods of time. G. S. had 11 determinations over a 4 mos.' period of observation. 4. Duplicate determina-

TABLE III

J.E.	143	143	143	142.5	145	146	148.5	145	146.5	144	145	145.5
W.M.K.	146	149	150	—	153	153	153	153	—	148	149	148
G.S.	146	143	144	146	147	147	145.5	142.5	146.5	146.5	144	148.5

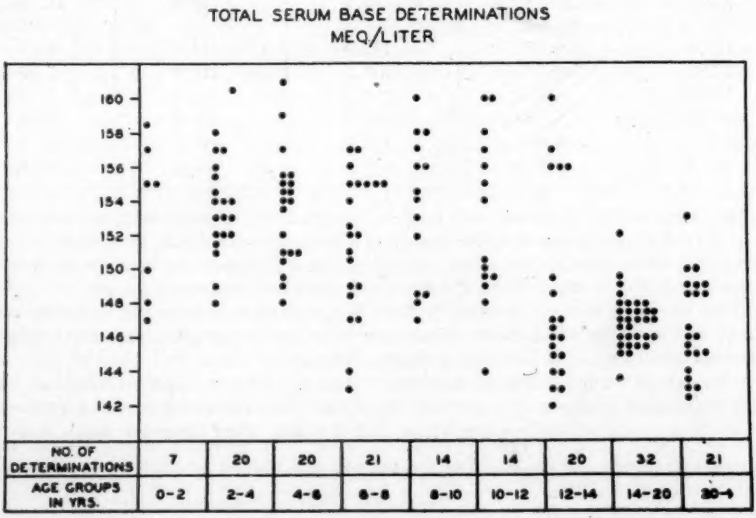

CHART 1

tions on single specimens were made on 50 consecutive samples. The deviations in these samples were never greater than 2 mEq./l. 5. The values obtained in the adults compared with those reported by Sunderman.[6]

Results

The values for total serum base in different age groups are shown in Chart 1. Almost all of the samples obtained in the pediatric age group were from well ambulatory children from an orphanage. A few samples were obtained from convalescent poliomyelitis patients. The samples from adults were obtained from internes, nurses and laboratory workers. In no case was there any suspicion that the individual had a disease process known to affect electrolyte balance. Unfortunately it was not possible to draw the blood under basal conditions. The adult values of 142 to 160.5 mEq./l. check closely with those obtained by Sunderman.[6] In children values of 143 to 160.5 mEq./l. were found to compare with those of other workers using different methods. Darrow and Hartmann[8] found

TABLE IV

Age in Yrs.	0–2	2–4	4–6	6–8	8–12	12–14	14 and older
No. of Determinations	7	20	20	21	28	20	53
Mean	152.9	153.7	153.5	151.6	153.2	148.3	146.84
Standard Deviation	±4.23	±2.24	±3.24	±4.68	±4.44	±5.39	±2.12

values ranging from 147 to 159 mEq./l. in 10 children. This compared with values of 145 to 151 mEq./l. in 3 adults. The benzidine method was used. Blackfan and Hamilton[9] reported figures of 156 to 162 mEq./l. in 9 normal children. Hamilton[10] determined total serum base values in 13 children with various pathologic states. His values varied from 140 to 166 mEq./l.

A statistical study was made of the 169 normal determinations.* Standard deviations for each group age are shown in Table IV. These deviations indicate that the range of values are within the expected limit of variation. Comparisons were made between 4 age groups. The "t" value for comparison between all values below the age of 12 and for the older group was 10.03. The "t" value for comparison between all values below the age of 12 and all older than 14 yrs. was 10.66. This would indicate a highly significant difference in total base in the 2 age groups. Comparisons of the 12 to 14 group and the older group gave a "t" value of 1.704 which is not significant. Comparison of the 8 to 12 group with the 12 to 14 group gave a "t" value of 3.387 which is highly significant. The conclusion was that there was a statistically significant difference between the total base in children below 12 yrs. of age and the older age groups. It is obvious that the 12 to 14 age group is transitional but is considerably closer to the adult group than the 10 to 12 age group. A review of the literature failed to reveal a similar finding.

Discussion

The principle behind this method has been generally accepted and Sunderman's data strongly suggest that the values obtained by this method check closely with those obtained by another method.[7] Comparison to the total base with the total anions is difficult because of the variability in the undetermined organic acids. The authors have attempted to correlate the relative increase and decrease in cations and anions in a number of persons and have found a satisfactory correlation. None of the patients in these studies had disease processes known to result in phosphate retention. The one patient with an inability to retain fixed base had normal serum phosphorus levels. Examples of these data are given in Table V.

The advantages of this method are considerable. Since the serum is not altered by the determination it may be used for other studies. This permits use of small quantities of serum, and the determination may be run in a matter of minutes. Reproducible results

* Statistical studies were made by Dr. C. Nash Herndon.

TABLE V

Patient	CO_2 C.P. mEq./l.	Cl mEq./l.	Urinary Ketones	Total Serum Protein Gm./100 cc.	Total Base mEq./l.	Estimated Changes In	
						Cations mEq./l.	Anions mEq./l.
1. B.H. 2 mos. Diarrhea	7.7	117.0	None	6.8	154.3		
	17.0	94.3	None	4.8	138.3	−16.0	−17.4
	15.5	87.0	None	6.1	135.3	− 3.0	− 4.8
	24.8	87.4	None	6.6	143.7	+ 8.0	+ 9.7
2. F.P. 11 mos. Renal Disease	8.2	106.0	None	5.9	145.8		
	12.2	109.0	None	5.2	152.0	+ 6.2	+ 7.0
	12.6	107.6	None	6.0	147.2	− 4.8	− 2.0
	22.0	96.0	None	5.4	146.0	− 1.2	− 2.2
	17.6	98.0	None	5.8	145.0	− 1.0	− 2.4
	20.3	100.0	None	6.1	148.2	+ 3.2	+ 4.7
3. H.E. 45 yrs. Normal	21.0	103.0	None	5.7	143.0		
	27.0	93.0	None	5.8	143.0	0.0	− 2.0
	21.0	90.0	None	7.3	145.0	+ 2.0	− 6.5
	21.0	99.0	None	6.5	148.5	+ 3.5	+ 7.0
	22.0	95.0	None	5.5	146.5	− 2.0	− 5.0
	21.0	94.0	None	5.9	145.0	− 1.5	− 2.0
	25.5	90.0	None	5.1	145.5	+ 0.5	− 0.5

have been obtained by relatively inexperienced technicians, and the equipment is not expensive.

The determination has been used as a rough check on the serum sodium level, and as such has served as a guide in the diagnosis of diseases involving sodium metabolism. It has been of aid in guiding therapy involving the use of sodium salts. In unusual conditions involving electrolyte imbalances the determination of total base by this method has served as a check on the sum of the anions. In many cases where routine determinations of serum chloride and CO_2 C. P. have been unusual the total base has aided in checking these data. Patients with alkalosis associated with vomiting and achlorhydria and hyperelectrolytemia serve as examples. The total base has not been the final answer but has been a simple means for indicating the need for more exact studies. Examples of such cases are given in Table V.

Conclusion

Values for total serum base in 96 normal children under 12 years of age as determined by the conductivity method fell between 143 to 160.5 mEq./l. The mean was 153. Standard deviations for each age group are given.

The values in 73 normal persons above the age of 12 varied from 142 to 160.5 mEq./l. The mean was 147 mEq./l. A statistically significant difference between the total serum base in children and adults was found.

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SPANISH ABSTRACT

Observaciones de Base de Suero Total en Niños y Adultos Jóvenes por un Método de Conductividad

Los valores de base de suero total en 96 niños normales de menos de 12 años de edad determinados por el método de conductividad bajaron entre 143 a 160.5 mEq./1. El medio fué 153. Se dan las desviaciones regulares de cada grupo de edad.

Los valores en 73 personas normales de más de 12 años de edad variaron de 142 a 160.5 mEq./1. El medio fué 147 mEq./1. Se encontró una diferencia estadisticamente significativa entre la base de suero total en los niños y en los adultos.

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EARLY TREATMENT OF METATARSUS VARUS (ADDUCTUS)

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THE purpose of this report is to call attention to a congenital deformity which is an important orthopedic problem. There has apparently been only one contribution on this deformity (Baker[1]) since Peabody's comprehensive article in 1933.[2]

Metatarsus adductus was characterized by Cramer[3,4] as early as 1904 as an adduction of the forefoot, along with a valgus position of the hindfoot. Dengler[5] emphasized that the term "metatarsus varus" describes a small subgroup in which the hindfoot is in valgus. He believed that "little children" show first a normal position of the calcaneus, without divergence of the rays of the astragalus and calcaneus until they begin to walk, when the calcaneus becomes "angulated" so that the hindfoot is then pronated.

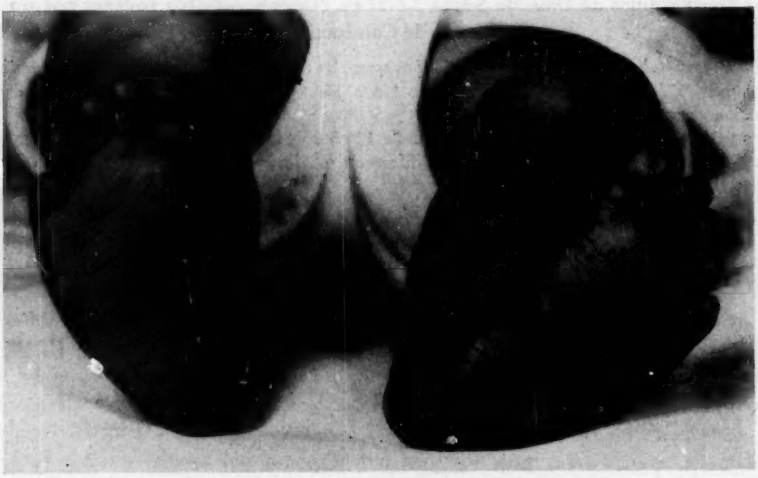

FIG. 1. VR, aged 7 mos. Metatarsus varus, severe, bilateral. Note adducted forefoot, rounding of outer border of foot and normal hindfoot.

Kuh[6] considered the condition to be congenital anomaly of the single bones of the tarsus, mainly of the scaphoid and first cuneiform, combined with an irregular curvature of the metatarsal bones. He alluded also to the frequent association of a pes cavus deformity. He described the strongly broadened foot in the region of the metatarsophalangeal joints, commonly known as "splayfoot." He pointed out further that the entire picture could simulate a clubfoot, were it not for the absence of hindfoot varus. Kuh apparently

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disagrees with the conception that a hindfoot valgus is a necessary feature of metatarsus varus. He stated that the Achilles tendon was usually in the midline. His description of the pathology in a late untreated case consisted of an outward luxation of the scaphoid, changes in the scapho-cuneiform joint, and morphologic changes in all the tarsal bones. Thickening of the first and fifth metatarsals occurred without bowing, whereas the middle three metatarsals show abnormal curvatures in their proximal portions. This curvature was not present at birth, but developed later, as the child began to walk.

This report is confined to the recognition and conservative treatment of metatarsus varus, or adductus, in children under two years of age. The deformity is limited to the forefoot, characterized by an adduction of the metatarsals, frequently with a splayfoot, a mild supination and some degree of cavus. Clinically, one notices the fixed adductus, a rounded outer border of the foot, palpable contraction of the medial fibers of the plantar

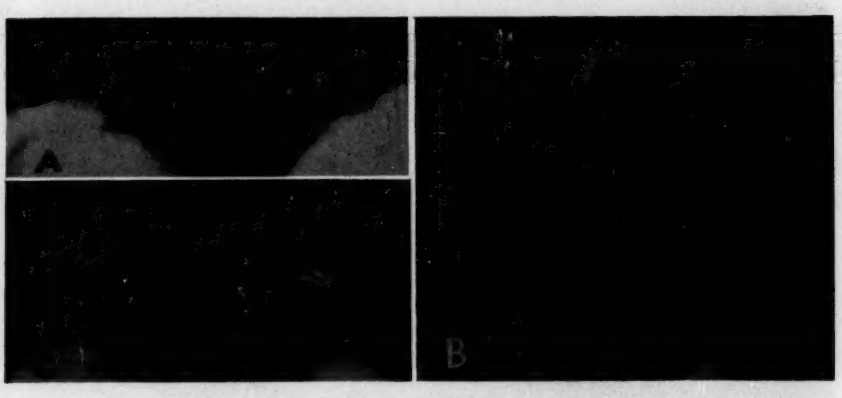

FIG. 2. A. Aged 3 mos. Note apparent bilateral adductus. B. Cavus in lateral view. C. Aged 17 mos. Note curving of metatarsals, adduction of forefoot, exhibiting progression of deformity in untreated case.

fascia, shortening of the tibialis posticus and at least some degree of supination of the forefoot, but with a normal hindfoot (Fig. 1).

Our observation of a normal hindfoot will bear discussion in light of Peabody's assertion that metatarsus varus is always associated with hindfoot pronation. We have not been able to substantiate this finding, although each of our 33 cases has been carefully examined in this respect. There has been no valgus of the heel, it always being held in a neutral position. We may be talking about different stages; perhaps there is no real discrepancy in this condition. The majority of our cases were preambulant and all were under 2 years of age, whereas Peabody described the pathology and treatment in a much older age group. Dengler asserted that the calcaneus does not go into valgus until sometime after the child begins to walk.

The evidence of splayfoot with associated metatarsus primus varus occurred in a high percentage of our cases. If this is accepted as the precursor of hallux valgus, then early recognition and adequate correction of this deformity would certainly seem justified. A "pigeon-toe" deformity would be corrected, utilizing a prophylactic measure to prevent "bunion formation" in later life.

The importance of early recognition and prompt correction should be emphasized. A

complete correction will be more readily obtained in the earlier months of life and the problem of early recognition lies in the hands of the pediatrician or family doctor. The postnatal examination may be the only time that the feet are examined and a real deformity may be overlooked until the child attempts to walk. The recognition of the deformity and the assumption that it is merely attitudinal and self correctible is a greater error.

This fallacy may be illustrated by the following case report (Figs. 2A, B and C). An infant 3 months of age was found to have a foot deformity. Manipulation of the feet was carried out until the child was 17 months of age. Roentgenograms made at the time of the original examination made possible comparative studies of an untreated case. There

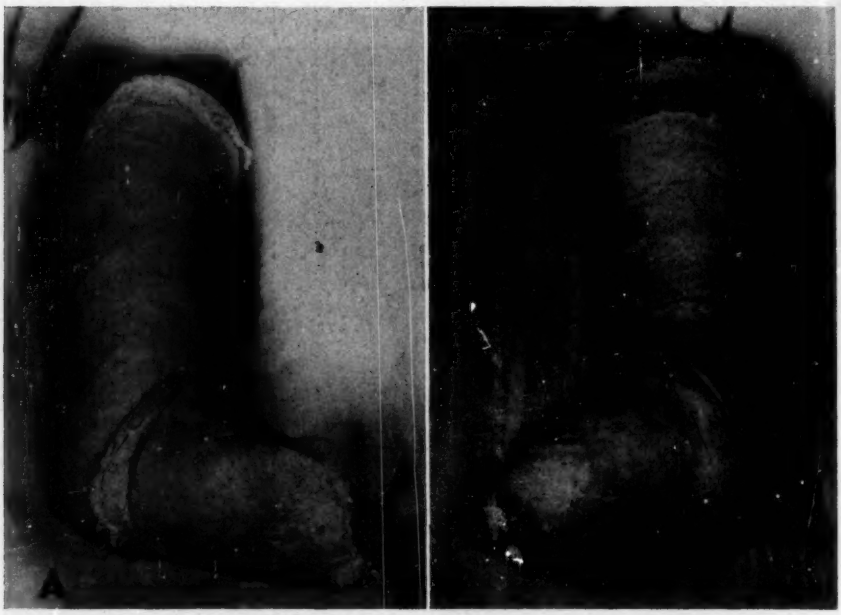

FIG. 3. A. Kite cast. Note lateral wedge. B. Kite cast. Medial split.

has been no improvement during this 14 mo. interval. The persistence of an adducted forefoot in an infant should always call for an orthopedic evaluation.

Roentgenographic studies are indicated in all cases even though the diagnosis is self-evident. The degree of deformity, the amount of splayfoot, the bowing of the metatarsal rays and the degree of hindfoot divergence should be compared with the degree of final correction. Routine roentgenograms of the pelvis should be made at the first examination, too, for three cases of congenital dislocation of the hips in infants under 6 mos. of age have been recognized by this procedure.

The methods in common usage may be mentioned and the technic used described. Reversing the shoes is ineffectual as an initial treatment. This is not done until the child becomes ambulant and by that time the adductus becomes fixed and requires a more

active type of correction. Little hope can be expected of overcoming a contracted fascia or a shortened tendon by corrective shoes.

Multiple strapping with adhesive or elastoplast has been tried in cases of mild deformity. It does not maintain correction for longer than a few days and has the further disadvantage of possibly excoriating or blistering the skin. Some of these objections apply also to the use of the Dennis-Browne splint. It may have some value for maintaining position after correction has been obtained but is not as practical as the plaster cast.

Multiple cast changes with repeated manipulations have been tried and found only partially effective. However, the multiple wedge-case method, patterned after Kite, has

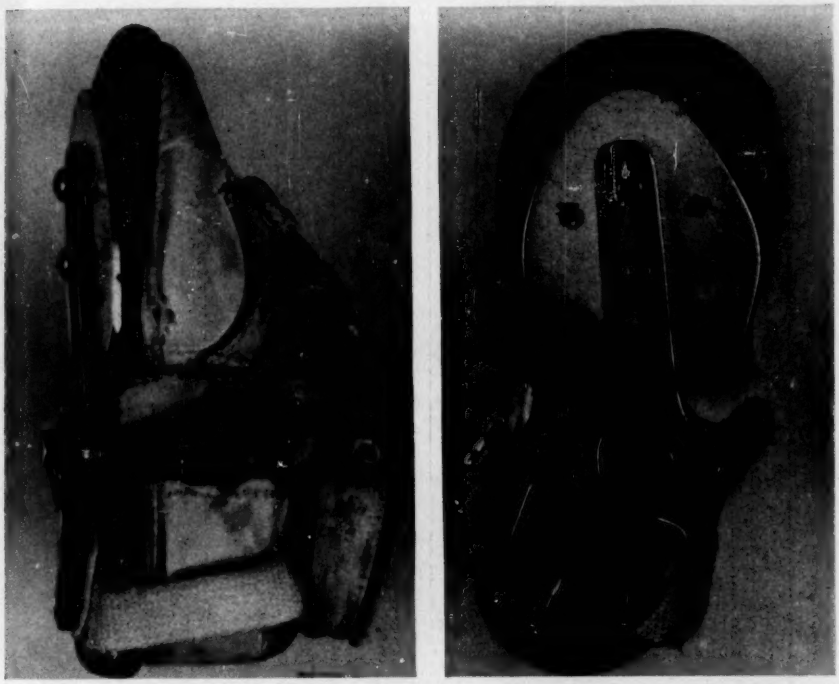

FIG. 4. Night splint. Adjustable ratchet at midtarsal joint with ankle strap to maintain hindfoot relationship.

been used in all cases and is now a routine procedure. This method has many advantages and will produce the maximum result in a minimal period of time. Correction can be obtained readily, even in the most resistant cases. In fact, this procedure is so efficient that the danger of overcorrection must be borne in mind.

A closely fitted case with a minimum of padding is now in use. Elastoplast, in strips and applied in basket-weave fashion, was used in the first few cases. This was changed to biased stockinette wrapped as a spiral bandage over a thin coat of tincture of benzoin. This is simpler, less expensive, and protects the occasional individual who is sensitive to elastoplast or adhesive. Small squares of thin felt are placed medial to the head of the first metatarsal and at the site of the lateral wedge; otherwise no padding is used. A

TABLE I

Name	Age (Mos.)	Diagnosis	Treatment		Wedge shoes	Period of Observation	Correction	
			Wedge casts	Corrective shoes (ratchet)			Roentgenogram	Clinical
RB	7	Adductus bilat. with cavus, left. Splayfoot, right	3 mos.	No	Yes	10 mos.	Complete	Excellent
KB	11	Adductus, right Varus, left	2½ mos.	Yes	Yes	2 yrs.	Complete	Excellent
SC	12	Adductus, left	Wedge casts	Still under treatment	—	—	—	—
SB	10	Varus, bilat. with cavus	Wedge casts	Still under treatment	—	—	—	—
JC	4	Varus, bilat. with cavus	2½ mos.	Yes	Yes	16 mos.	Partial	Partial
BC	6½	Varus, bilat. severe	2½ mos.	Yes	Yes	2 yrs.	Complete	Good, mod. hallux varus
SC	15	Adductus, mod. left	3 mos.	No	Yes	4 mos.	Complete	Yes
SC	3 dys.	Adductus, bilat. Mod. severe, right	2 mos.	Yes	Yes	16 mos.	Complete	Excellent
JC	12	Adductus, left moderate	2 mos.	2 mos.	Yes	20 mos.	Complete	Excellent
PD	7	Adductus, right moderate	3 mos.	No	Yes	8 mos.	Complete	Excellent
WF	4½	Adductus, left	3½ mos.	Yes	Yes	14 mos.	Complete	Excellent
PH	5	Varus, unilat.	2 mos.	Yes	Yes	20 mos.	Complete	Excellent
RH	3 wks.	Varus, very severe right. Mod. left.	4 mos.	Yes	Yes	18 mos.	Complete	Over correction, left.
JH	13	Adductus, bilat. moderate	6 wks.	Yes	Yes	15 mos.	Complete	Residual tibial torsion.
JJ	4	Varus, left Adductus, right, moderate	2 mos.	Yes	Yes	20 mos.	Complete	Complete
DK	6	Adductus, bilat. severe. Splayfeet	5½ mos.	No	Yes	13 mos.	Good, slight hallux varus	Good, slight hallux varus
KK	13	Adductus, bilat. moderate	5 mos.	Yes	Yes	12 mos.	Complete	Excellent
BK	4	Adductus, severe right Calcaneo-valgus, left	2 mos.	No	Yes	11 mos.	Complete	Excellent
SL	3	Varus, bilat mod.	2 mos.	Yes	Yes	22 mos.	Complete	Excellent
CMc	8	Adductus, bilat. severe	2½ mos.	Yes	Yes	17 mos.	Complete	Excellent
MN	6	Varus, bilat. severe	2½ mos.	Yes	No	16 mos.	Complete	Excellent
SR	12	Adductus, bilat. severe	Wedge casts	Still under treatment	—	—	—	—
VR	7	Varus, bilat. severe	3½ mos. Off 3 wks. No recurrence.	No	Yes	1 yr.	Complete	Excellent
AS	4	Varus, right Adductus, left	Casts for 3 mos. 2 mos. Recur. in 2 wks. on right. New casts for 1 mo. Recur. again. Rewedge for 1 mo.	Yes	Yes	10 mos.	Complete	Excellent
JS	8	Adductus, bilat. moderate	3 mos.	No	Yes	6 mos.	Complete	Excellent
AS	13	Adductus, severe	2½ mos.	Yes	Yes	18 mos.	Complete	Excellent
PS	3	Varus, unilat.	2½ mos.	Yes	Yes	14 mos.	Complete	Excellent
JT	9	Adductus, unilat.	3 mos. Recur. in 1 mo. New casts for 6 wks.	Yes	Yes	15 mos.	Complete	Excellent Tibial torsion
TW	8	Adductus, severe with cavus unilat.	2½ mos.	Yes	Yes	2 yrs.	Complete	Excellent
JZ	9	Adductus, left. Calcaneo-valgus, right.	2½ mos.	Yes	Yes	2 yrs.	Complete	Excellent

short leg cast is quite adequate unless some associated deformity (tibial torsion, genu valgum) is being corrected simultaneously. Only a few of the casts have slipped distally requiring reapplication. Weekly wedging is then performed using dorsal and plantar hinges (Figs. 3A and B). It is necessary to change the cast every third or fourth week and the gradual wedging again instituted. This process of correction requires a period of 10 to 12 weeks, depending upon the age of the child and the severity of the deformity.

Several cases of recurrence, while under observation during the first postcorrection month, have been observed. These have responded to an additional series of wedging, indicating that the original correction was probably incomplete. Criteria, either clinical or by roentgenogram, to determine when correction is complete or will be maintained are

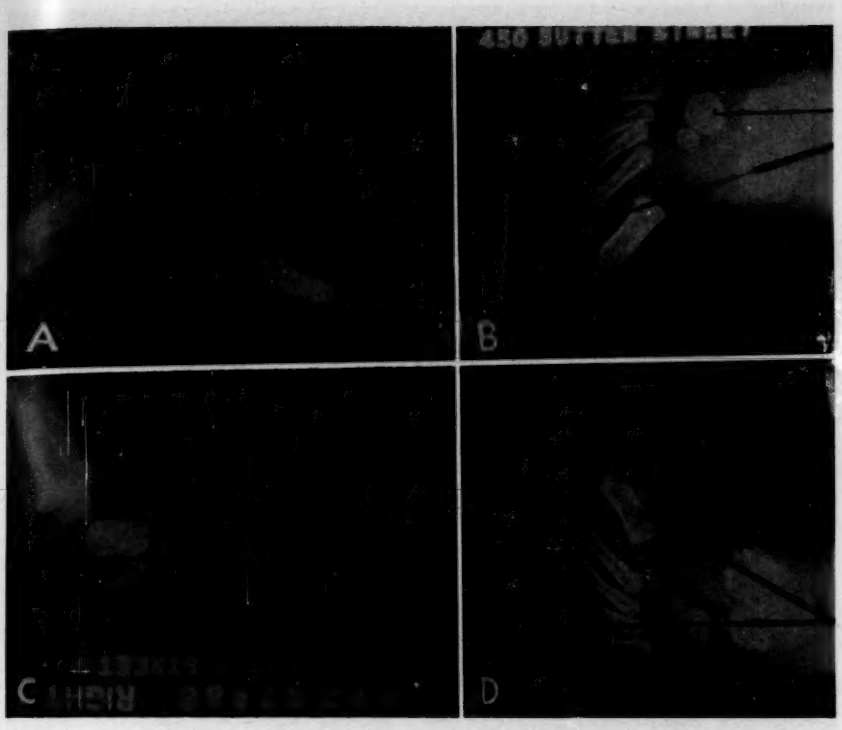

FIG. 5A, B, C and D. CMc. Aged 8 mos. Adductus, bilateral, severe.

FIG. 5E. CMc. Four months after correction.

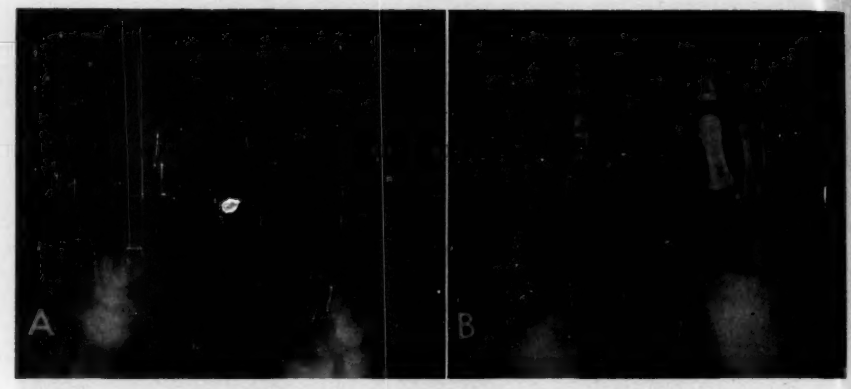

FIG. 6. AS. A. Aged 4 mos. Adductus, severe, unilateral. B. 6 mos. after correction.

FIG. 7A

FIG. 7B

FIG. 7A. VR. Aged 7 mos. Metatarsus, varus, bilateral, severe.
FIG. 7B. VR. Note curving of metatarsals.
FIG. 7C. VR. Five months after correction. D. Wt. bearing view 1 yr. later.

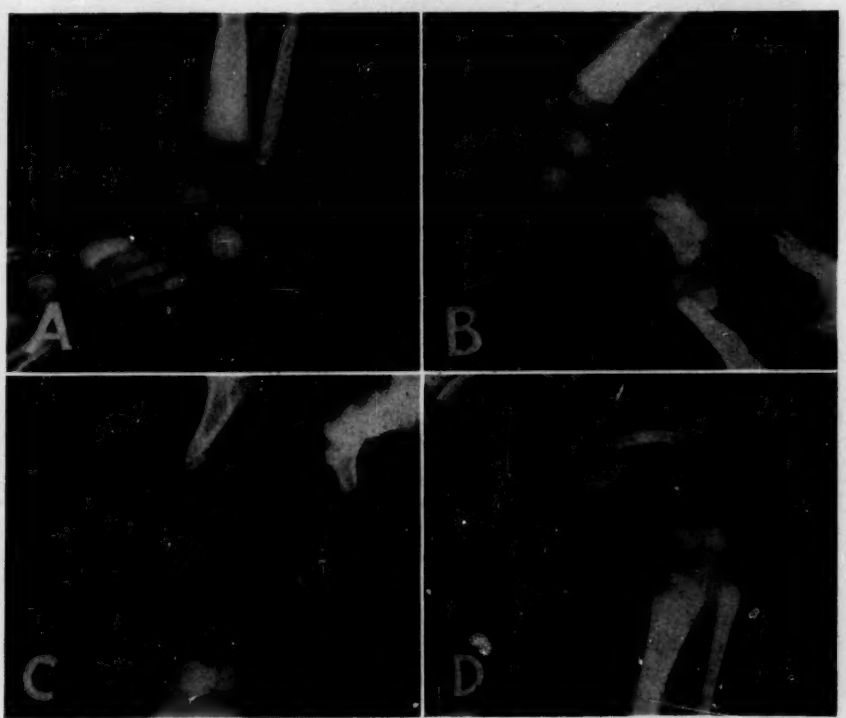

FIG. 8A, B, C and D. RH. Aged 3 wks. Metatarsus varus, severe, much more marked on right. Note superimposition of 2nd, 3rd and 4th metatarsal rays.

not clear. A variety of postcorrection appliances to follow the wedge-cast have been employed. A split shoe, with a Dennis-Browne ratchet applied to the sole and adjustable as to the degree of abduction, was devised for the nonwalker and as a night splint in the older child (Fig. 4). For the walking child, a simple corrective shoe has been devised

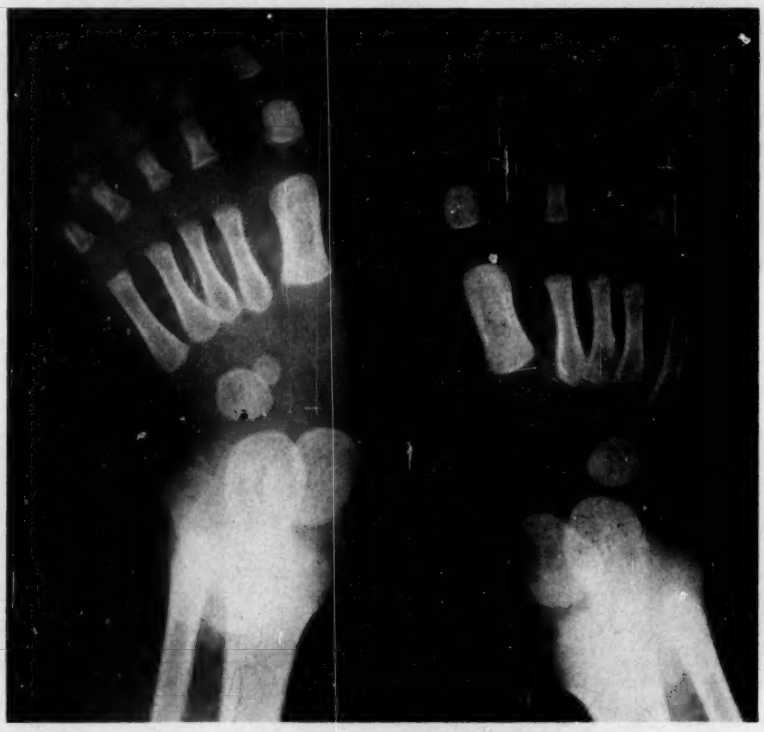

FIG. 8E. RH. After correction. Note moderate abduction of left forefoot, indicating overcorrection.

which employs the same principle, especially where correction is complete and further adjustment is unnecessary. An outer sole patch to overcome any tendency to recurrence of supination may be used as a final follow-up. An inner heel wedge is used also to overcome any tendency to valgus which may result from the corrective wedging. The necessity of any of these appliances to maintain correction may have little value in preventing recurrence of the deformity in the occasional case. Recurrence demands rewedging.

A series of 33 cases were observed: 20 were bilateral and 13 unilateral deformities (Table I).

Eighteen cases were in females and 15 in males, a reversal of the incidence accepted in ordinary clubfoot. The average age of the patients when brought in for treatment was 7½ mos.; the youngest was 2 mos. and the oldest 15. A total of 54 feet were treated, 34 classified as adductus and 20 as varus deformities. A diagnosis of a varus deformity was based on extreme rounding of the outer border of the foot, supination of the forefoot, marked contraction of the medial fibers of the plantar fascia, and the roentgeno-

graphic finding of extreme curving of the metatarsals. A lesser degree of deformity was termed "adductus." The average length of time necessary to gain correction was 3 mos. The average period of observation was 15 months.

Of the 54 feet treated, 46 were considered to be corrected and maintained. There was one overcorrection with a valgus of the heel and an abducted forefoot. One case remains improved, but not fully corrected. Seven are recent cases and still under treatment.

Illustrations from the series are presented in Figs. 5 to 8.

Conclusion

Early recognition and treatment of a common deformity of the foot in infants is urged.

The pathology of metatarsus varus has been described, emphasizing the normal hindfoot in the pre-ambulant child. Metatarsus varus may be the precursor of a late hallux valgus deformity. The most efficient method of treatment is the use of wedge casts. None of the cases reported required operative procedures for correction.

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Spanish Abstract

Temprano Tratamiento de Metatarsus Varus (Adductus)

El temprano diagnóstico de metatarsus varus dará resultados uniformente buenos mediante medidas ortopédicas conservativas. Se caracteriza por la aducción fija de la parte delantera del pie, un borde exterior redondeado del pie, frecuente asociación de pies planos y cierto grado de cavus. La parte trasera del pie es normal en el niño preambulante, pero se puede convertir en pie zambo en el niño mayor. Los estudios Roentgen antes y después de la corrección con un auxiliar necesario en el tratamiento. Esta deformidad no se corrige por si sola y requiere terapia definida.

El tratamiento más eficaz es una técnica de molde de cuña múltiple. La corrección se obtiene en 10 ó 12 semanas y generalmente no se necesitan aparatos para mantener la corrección después de eso. Se han registrado 33 casos, 20 con deformidades bilaterales. Las hembras predominan un poco en estas series, lo que es el contrario del caso en pie de piña. Se ha obtenido la corrección de la deformidad en todos los casos, con la excepción de uno, mediante medidas ortopédicas conservativas.

450 Sutter Street

MERCURY POISONING FROM CALOMEL PRODUCING SUBACUTE ACRODYNIA AND ITS TREATMENT WITH DIMERCAPROL

Report of a Case

By HUGH A. CARITHERS, M.D.
Jacksonville, Fla.

MERCURY poisoning is not uncommon. Calomel as a cause is, however, rare, not only because the drug is infrequently used in modern therapy but also because its toxicity is largely independent of the size of the dose. McNally[1] reported the death of a 2 year old child within 24 hours of ingestion of 1.6 gm. of calomel. Webster[2] stated that a boy of 14 years died following the ingestion of 0.36 gm. of the drug. Le Clerc[3] and Runeberg[4] also reported fatal cases after large doses.

Evidence that acrodynia may be associated with appreciable amounts of mercury in the urine has been demonstrated by Warkany.[5] Cases of this disease following ingestion of mercury were recently reported by Bivings and Lewis[6] and by Elmore.[7] In Bivings and Lewis' case the patient had been given mercurous chloride (calomel) and rhubarb, and in Elmore's two cases teething powders, each of which contained 3.5 mg. of calomel. This preparation is widely used in some sections of the United States, the trade name being "Dr. Moffett's Teethina Powders."*

That heavy metals, arsenic, mercury and gold, will form more stable compounds with dimercaprol (BAL) than with tissue proteins and cellular enzymes, thus hastening elimination from the body, has been well established. Longcope and Luetscher[8] treated 23 patients with BAL following the ingestion of mercury bichloride, with death in only one case. Dimercaprol was used in treatment by Bivings and Lewis[6] and by Elmore[7] with dramatic improvement in the symptoms of acrodynia.

The case of mercury poisoning presented here may represent a pre-acrodynic state, showing many, but lacking some, of the characteristics of the disease.

CASE REPORT

G. A., a girl, was first seen at the age of 6 mos. with the chief complaint of "weak eyes." She was the only child of a 21 yr. old mother; family history was noncontributory. Birth wt. was 4.3 kg. and delivery normal. She had been given evaporated milk formulae since birth. Vitamin complements had been started at 1 mo. and cereals, fruits and vegetables at 3 mos.

Child had been well until restlessness, attributed to teething, developed at 4 mos. of age. "Teethina Powders" were given from that time until she first was brought to this office, starting with ½ powder in the morning and ½ in the afternoon. Later a whole powder was used as a dose. They were given intermittently, 4 or 5 days regularly with 2 or 3 days' rest in between. Ten days before

(Received for publication Feb. 10, 1949.)

* Manufactured by the C. J. Moffett Medicine Co., Columbus, Ga. The company manager stated that the powders are sold throughout the United States, but that the volume of sales in the South is greater than elsewhere. In 1933, action of the Federal Trade Commission resulted in a consent Cease and Desist Order, wherein the concern was ordered to discontinue such misrepresentation in its advertising of the product as that the formula was prepared by a baby specialist or had been in use for three generations, or had been endorsed by doctors and nurses.

the patient was examined, lethargy alternating with restlessness of considerable degree was noted. Eyes appeared weak and in a few days she would not open her eyes outdoors and turned her head away from a window when indoors. She was taken to an ophthalmologist, who could find no cause for the photophobia. Temperature, checked once, was 37.7° C.

Five days before patient was brought here for observation, a rash developed on the head. There were discrete papules at first, but some soon became pustular. Another physician had prescribed a sulfonamide, which did not seem to cause local or general improvement after 48 hrs. It was noted at this time that she had lost 240 gm. in wt. She was admitted to St. Vincent's Hospital.

Physical Examination: Patient was a restless white infant girl, well developed and plump, but with strikingly flabby musculature. Pulse rate was 140/min., respirations were 47/min. and blood pressure was 118 systolic and 88 diastolic. She had pronounced photophobia, holding her face against her mother's neck or holding the backs of her hands pressed against her eyes if carried to a window. There was present a maculopapular rash on the head only, with a smooth, flat erythematous lesion about 3 cm. in diameter on the left brow and another of the same size just proximal to the left ankle. There was no erythema of the hands and feet and no desquamation. Fontanel was under normal tension and of normal size for her age. Eyes, except for photophobia, showed no abnormalities, there being no conjunctivitis or abnormal pupillary reaction. Examination after use of a mydriatic showed normal eyegrounds.

In the mouth there were no abnormalities; 2 lower central incisors were present and no evidence of infection, lead or mercury line, or salivation was noted. Ear canals and drums appeared normal. Chest was symmetric. Lungs were clear and resonant. Heart rate was variable, from 90 to 140/min. Heart sounds were of good force and there were no murmurs. Abdominal musculature was markedly flabby and there were no masses or tenderness. Liver was not palpable and the tip of the spleen barely so. Genitalia were normal. Extremities were normal except for lack of muscle tone. Reflexes showed no abnormalities.

Laboratory Data and Roentgen Examination: Blood Kahn test gave negative results. Blood cell count was Hgb. 12.1 gm./100 cc., RBC 4.1 million/cmm. and WBC 8.1 thousand/cmm. with segmented neutrophils 39%, juveniles 9%, lymphocytes 46%, monocytes 4%, eosinophils 1% and basophils 1%. Several routine urinalyses showed no abnormalities. Examination of the stool for ova and parasites gave negative results. Reaction to a tuberculin patch test was negative. The day after admission, a specimen of urine collected in a mercury-free container showed a mercury content of 0.33 mg./l. This high figure was reduced to 0.21 mg./l. in a specimen collected 8 days after admission. Eleven days after admission a specimen showed 0.05 mg./l. Roentgenogram of the long bones showed normal growth and development for the age of 6 mos. Slight decalcification was evident.

Treatment: The day following admission, a 10% solution of BAL in peanut oil was started. For 5 days patient received 0.2 cc. every 4 hrs. intramuscularly. On the 6th day, the same dosage was given every 8 hrs. and on the 7th day every 12 hrs. Total dosage of the drug was 0.86 gm. Because of the pustular rash, penicillin 300,000 u. in oily solution was given daily, beginning on the 6th day and continuing until discharge. Full feedings with vitamin complements were given throughout the period of hospitalization.

Course in Hospital: The great irritability and anorexia noted during the 1st few days of the patient's 13 day hospital stay quickly improved. Wt. on admission was 7.5 kg. By the 6th day it was 7.8 kg. Photophobia improved slowly but was still present, to a slight degree, on discharge. Skin condition became worse after admission, more of the papules on the head becoming pustular. This cleared after penicillin was started on the 5th hospital day. The large, flat erythematous lesions, which may have been exaggerated reaction to insect bites, disappeared after a few days. At no time was there fever and the blood pressure at the time of admission was the highest recorded. Child sat alone, for the first time, toward the end of her hospital stay.

Follow-Up: When seen 2 wks. after discharge, patient still had photophobia to a moderate degree, although it had been noted that at times it seemed to be absent. There was slight desquamation of the tips of the fingers. Child had recovered from a severe infection of the upper part of the respiratory tract, which was noted the day after discharge from the hospital. She had gained only 0.17 kg. during the 2 wks. at home. Thereafter, she rapidly lost all evidence of illness and 1 mo. after discharge all evidence of photophobia had disappeared. She became cheerful, ate well and at the age of 8 mos. weighed 8.4 kg.

Discussion

The history of ingestion of mercury, even though in a form usually nontoxic, combined with the finding of large amounts of the drug in the urine makes the diagnosis of mercury poisoning in this case tenable. The reason that chronic poisoning from calomel was not observed frequently during those years when its use was popular may be because it was used only for brief periods as a purge. Even when it is given in teething powders, two months of almost steady dosage would be unusual. This patient may have been given some powders that had undergone conversion or deterioration. Prolonged exposure to sunlight converts mercurous chloride (calomel) to mercuric chloride and metallic mercury. Such a conversion is also effected by chlorine water, nitrohydrochloric acid, and, to a less extent, hydrochloric acid and alkaline chlorides. Many of the signs of mercurous chloride poisoning, whether acute or chronic, were missing in this case. There was no excessive salivation, nor were there lesions in the mouth. Urinalyses revealed none of the

TABLE I

Acrodynia Observed in Florida by Group of Pediatricians

Pediatrician	Location	Yrs. in Practice	Cases
Boulware	Lakeland	18	2
Cook	Tampa	23	2
Gachet	Lakeland	8	1
Hayes	Jacksonville	18	2*
Hitchcock	Orlando	9	0
Holloway	Jacksonville	31	0
Martin	Tampa	26	0
McKibben	Miami	25	3*
Palmer	Jacksonville	18	0
Quillian	Coral Gables	22	1†
Rudolph	St. Petersburg	24	0
Von Meysenbug	Daytona Beach	13	1
Willis	Coral Gables	12	1*
		—	—
	Total	247	13
	Visitors		6
			—
	Floridians		7

* Out of state visitors.

† Child had just returned after spending several months in the state of Washington.

usual signs of renal damage. Diarrhea and vomiting were absent and there was no reason to suspect abdominal pains. Present, however, were anorexia, weight loss, irritability, muscle weakness and a skin rash.

While pointing out that acrodynia may occur in all grades of severity, Bilderback[9] stated that the disease is a specific one, "as clear-cut and definite as pneumonia or meningitis." In this case there occurred no erythema of the hands and feet, no excessive sweating and no oral lesions; the rash, while compatible with acrodynia, was not typical. Nevertheless, the pronounced photophobia, combined with slight hypertension and the other signs described, more strongly suggests this disease than any other. The term "pre-acrodynic state" seems feasible in describing this case.

Perhaps longer exposure to mercury would have produced a more clearcut picture. It is well known that acrodynia occurs much more commonly in some areas than in others, and environmental or climatic factors may have prevented its full expression in this case. The disease is rare in the locality from which the patient came, as shown in Table I.

The response to treatment with BAL was not dramatic. After seven days of treatment with what may be considered, at the present time, a large total dosage, the child was less irritable and was gaining weight, but photophobia, while less severe, was still present after four weeks. The individual dose of BAL was calculated on the basis of 2.5 mg./kg. per dose, and was given for 43 doses rather than for 32, the number used by Elmore.[7] No toxicity was noted. No novocain was used before injection and nurses reported no more pain response after BAL than after penicillin. Eagle,[10] in treating arsenic poisoning with BAL, suggested a dosage schedule based on 3 mg./kg. While the optimal dosage in children is not known, it is suggested that larger amounts might be tried cautiously.

Summary

A 6 month old child received calomel in teething powders over a two months' period. Symptoms suggestive of acrodynia developed. BAL was effective in treatment.

Acknowledgment

Appreciation is expressed to Dr. Josef Warkany and Mr. D. M. Hubbard of the Children's Hospital Research Foundation, Cincinnati, for the urinary mercury determinations.

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Spanish Abstract

Envenenamiento de Mercurio del Calomel Produciendo Acrodinia Subaguda y Su Tratamiento con Dimercarprol; Relato de un Caso

A una niñita de 6 meses se le había dado cloruro mercurioso en polvos de dentición (un producto llamado "Dr. Moffett's Teethina Powders" comunmente usado en algunas partes de los Estados Unidos) por dos meses antes de que se viera con la queja principal de fotofobia. Estaba irritable, tenía masculatura floja, un sarpullido máculopapuloso en la cabeza y ligera hipertensión, y había perdido peso.

Se le dió dimercaprol (BAL), basando la dosis individual en 2.5 mg./kg. de una solución de 10%

de la droga en aceite de cacahuete. Se le dieron seis dosis diarias los cinco primeros días, tres dosis el sexto día y dos dosis el septimo día. La cantidad total de la droga usada fue 0.86 gm. Se puso menos irritable y aumentó peso; el sarpullido desapareció, pero la fotofobia persistió a un grado menor por un mes después del tratamiento.

Muchas de las señas observadas en el paciente sugieren acrodinia. No había, sin embargo, rojura en las manos y pies, ni excesivo sudor ni lesiones orales.

2000 Park Street

ERRATUM

Veghelyi, P. V., Pancreatic Function in Scarlet Fever, PEDIATRICS **4**:94, 1949.
Page 95, the following table should be substituted.

TABLE I

Enzyme	Method	Limit of Normal Range		Unit
		Lowest	Highest	
Amylase	Wohlgemuth[7]	160	2048	dilution
	Ågren and Lagerlöf[8]	0.33	2.45	gm. maltose/ml. of juice
Trypsin	Michaelis[9]	128	1024	dilution
	Andersen and Early[10]	0.01	0.0025	dilution/Tubes nos. 4 and 2/
Lipase	Willstätter[11]	13	53	19.8 ml. n/10 KOH
	Freudenberg[12]	3.0	8.5	ml. of n/10 NaOH/5 ml. of milk 1 ml. solut. 2 hr.
Serum amylase	Somogyi[13]	60	200	original
Serum lipase	Cherry and Crandall[14]	0.2	1.5	ml. of n/20 NaOH/ml. of serum

Page 97, legend for Figure 1 should read:

FIG. 1. Daily mean values of Table III.

(H unit means the upper limit of the normal range [see Table I]).

Page 99, under "Abbreviations," at the end of Table III, the line which reads "Per cent of the upper limit of normal; ordinary figures indicate per cent of lowest limit of normal," should read "Figures with an asterisk (*) are given in per cent of the upper limit of normal range; ordinary figures indicate per cent of lowest limit of normal."

Pediatrics

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AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

Round Table Discussion

MANAGEMENT OF VASCULAR NEVI

MAURICE J. COSTELLO, M.D., *New York City, Chairman*

Chairman Costello: The management of vascular nevi is of great interest to the pediatrician. He more than any other specialist, including the general practitioner, is first consulted regarding the advisability of treating a hemangioma and as to the best method of treatment which will insure a good therapeutic and cosmetic result. Since there appears to be no unanimity of opinion regarding these points, it was thought that a round table discussion by a small group would help us envision a better approach to this interesting and important problem.

Permit me to preface my remarks by stating that some pediatricians believe that the dermatologist and radiologist are apt to treat hemangiomas too early and that there are hemangiomas treated which would have disappeared spontaneously, this latter thought being influenced to a great extent by the report of Lister who claimed that superficial hemangiomas will disappear completely in the great majority of cases. The dermatologist and radiologist, on the other hand, believe that the pediatrician in some instances, because of the opinion expressed above, permits too long a time to elapse before treatment is instituted, thereby losing the golden opportunity for effective rapid permanent cure of these hemangiomas. There are arguments to be advanced in the substantiation of both opinions, and it is for this reason that we hope by free and open discussion to arrive at a more accurate answer to the questions which have been raised.

In this brief presentation it is hoped that I will be able to place in sharp relief all the important aspects of heredity or familial incidence of these lesions, the time of their occurrence, the types, their behavior and significance, the indicated type of therapy, and the results which may be accomplished in their proper treatment.

I shall take up the vascular nevi in the conventional order rather than the order of their importance. There are four types of localized telantiectasia or acquired hemangiomas consisting of small, usually multiple, lesions: 1. nevus araneus (spider nevus); 2. senile angioma (senile ectasia); 3. hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome); 4. pulsating spider nevi (pulsating telangiectasia, pulsating hemangioma).

From the Annual Meeting of the American Academy of Pediatrics, Atlantic City, N.J., Nov. 20, 1948.

Published without discussion.

Copies of a reference chart on "Management of Vascular Nevi" may be obtained from Dr. Maurice J. Costello, 140 East 54th Street, New York 22, N.Y.

Nevus Araneus (spider nevus): These lesions may be single (as the result of trauma such as picking a pimple) or multiple. The nevus is slightly raised, usually a pinhead sized punctum, from which several dilated capillaries radiate like the legs of a spider. When a number of lesions are present in childhood, it suggests hereditary causation. The lesions are usually present on the face but they may also be seen on the back of the hands, forearms, neck and occasionally upper part of the chest. They may become evident for the first time during pregnancy, or pre-existing lesions may increase in number and size at that time. They are usually observed in Rendu-Osler-Weber disease, hepatic diseases (especially cirrhosis of the liver caused by chronic alcoholism), scleroderma, cutaneous calcinosis and von Recklinghausen's disease. They can be differentiated from petechiae in that the latter disappear on diascopic pressure. Even in those patients who present but two or three spider nevi there may be personal or family history of frequent epistaxes resulting from ruptured spider nevi in the nasal mucous membranes.

Senile Angioma (senile ectasia): These are small pinhead to split pea sized, ruby colored, elevated, rounded lesions in the skin of adults, usually on the front of the torso. They represent clusters of dilated capillaries. They are usually multiple, may be numerous, cause no harm and are of no clinical significance. Treatment is not necessary. The pinpoint to pinhead sized lesions are to be differentiated from petechiae.

Hereditary Hemorrhagic Telangiectasia (Rendu-Osler-Weber disease): This disease is rather rare and consists of several to numerous small telangiectatic blood vessels of the skin and mucous membranes indistinguishable from spider nevi (nevus araneus). In addition to their appearance on the face, neck, upper part of chest, back of hands and forearms, they are also present on the mucous membranes of the nose, oral cavity including the lips, tongue, buccal mucous membrane, the esophagus, the stomach, the vulva and the scrotum. The lesions become evident at puberty and continue to increase in number thereafter. There is a remarkable occurrence in families. The cause is unknown, other than that there is an inherited weakness of the walls of the capillaries. The capillaries composing these nevi are dilated and have thin delicate walls composed of a single layer of endothelial cells. Epistaxes are frequent and it is for this reason that these patients seek medical advice. Profuse hemorrhages from ruptured nevi in nose or stomach may occur spontaneously or follow coughing or sneezing. There may be several hemorrhages a day, week or month. Hypochromic anemia is usually present. The tendency to hemorrhage is aided by the severity of the anemia. A considerable degree of physical disability may accompany the severe type. It is easily distinguished from hemophilia, thrombocytopenic purpura, aplastic anemia and acute leukemia by the usual laboratory tests and by the clinical picture.

Pulsating Nevus Araneus (spider nevus): These nevi are rare, turgescent and larger (the central bulb is elevated, measuring 2 to 5 mm.) than the nonpulsating type. The pulsation is usually observed with the naked eye or with the aid of the magnifying glass. The lesions occur on the upper part of the face around the eyes, back of the hands and upper part of the trunk. The importance of this type of hemangioma is its association with hepatic disease, hepatitis, jaundice or cirrhosis of the liver. These pulsating spider nevi may antidate the clinical evidence of hepatic disease and help to anticipate or confirm the diagnosis. A few cases have been associated with the lymphosarcoma and pregnancy.

Nevus Flammeus (port wine stain, form of capillary hemangioma): Histologic examination of this type of hemangioma indicates a narrow superficial band of numerous dilated capillaries composed of flattened adult endothelium. When extensive, port wine marks may extend to the extremities, especially the lower extremities, or they may be only one component of an extensive vascular anomaly. The common site for the port wine mark is the face, neck and upper part of the thorax, the nevus often being continuous. Zosteriform distribution on the extremities is not uncommon. The depth of the color, from strawberry red to that of slate color, depends upon the depth of the lesion, the degree of vascularity, and whether arterial or venous blood predominates. The lesion blanches on diascopic pressure. The mucous membranes of the mouth may be extensively involved, the thickness suggesting a hemangioma of the cavernous type in these locations. Some of the lesions are superficial, forming a pale pink discoloration of the skin, at times in "V" shape with the lower angle in the glabella region at the root of the nose, or at the nape of the neck. This type is usually accompanied by lighter staining of the upper eyelids and disappears by the end of the second year. Nevus simplex (Unna's nevus) in the nape of the neck may be found in one or both parents. In my experience, a patient presenting this type of nevus or any other vascular nevus is likely to give a history of frequent epistaxes in himself or in members of his family, or a family history of vascular nevi.

The port wine mark occurring in the nape of the neck is observed in about one third of the babies at birth. If it is superficial and light, it disappears in several years; if dark and deep, it remains throughout life.

Nevus Anemicus (nevus avasculosus): This is a white flat lesion on the niveau of the skin. It is sharply demarcated, and geographic in outline. This nevus is avascular. The lesions are usually found on the torso, especially the upper part of the back. They are usually smaller than palm sized. They are often confused with vitiligo but in the latter condition the border is hyperpigmented. The areas of hypopigmentation are usually multiple and become pink or red when rubbed, these features being absent in nevus anemicus. When the nevus anemicus is rubbed the white of the nevus becomes accentuated because the surrounding skin becomes pink or red.

Hemangiomas (raised and deep): These are benign lesions composed of newly formed blood vessels and they are not the result of hypertrophy nor of dilatation of pre-existing blood vessels. These tumors enlarge slowly and do not metastasize. They are congenital in origin and are believed to arise from embryonic sequestrations of mesodermal tissues. They evolve following the formation of projections of endothelial tissue which form solid cords, which later canalize and communicate with the antecedent vessel, but they do not communicate with surrounding normal vessels. According to the report of Watson and McCarthy, 73% of their patients presented evidence of hemangiomas at birth and over 85% during the first year. Many cavernous hemangiomas which allegedly did not appear until adult life had probably passed unnoticed until they began to enlarge or cause inconvenience. Hemangiomas are at least twice as common in females. They occur in other members of the family in about 15% of the cases. Hemangiomas which persist to adult life (again usually the deep type) increase in size at the onset of menstruation and during pregnancy. Superficial hemangiomas grow slowly and in relation to the growth of the infant. Twenty-five per cent of the patients have more than one lesion and different types of hemangioma may be represented in the same patient.

Superficial Hemangioma (strawberry mark) (capillary hemangioma): This lesion is circumscribed, elevated, strawberry to raspberry color, finely lobulated, compressible, blanches on pressure, and has a decided tendency to spontaneous recovery. Histologically, the lesion consists of a great number of dilated, closely aggregated capillaries with well formed endothelial walls and delicate tissue stroma. Elements of capillary hemangiomas may be found in hemangiofibromas and hemangiolipomas. Mixed capillary hemangiolymphangiomas are seen occasionally. Examination with the Wood fluorescent light may reveal superficial nevi which are not clearly visible to the naked eye. It helps to delineate the extent of the lesion. It is an aid in dermatologic diagnosis.

Cavernous Hemangiomas (deep hemangioma, nevus cavernosus): They are composed of masses of dilated thin walled vessels and blood sinuses lined with endothelium and distended with blood. Cavernous hemangiomas are situated in and beneath the skin, are irregular in outline, somewhat soft, and compressible. They form the most common type of hemangioma and are usually present at birth but, in a few instances, they may not be clinically evident until later in life, especially when they occur on the mucous membranes. They may increase slowly in size throughout life, at times attaining considerable size. Cavernous hemangiomas rarely disappear spontaneously. They may be multiple and may be found in any organ or structure of the body as well as the skin. This fact should always be kept in mind when children who present a hemangioma develop unusual symptoms which may be difficult to evaluate. They may occur on the face, neck, tongue, mucous surface of the cheeks and labia, extremities, liver and bones (particularly the vertebrae), stomach and intestine. They usually involve the skin, subcutaneous tissues and muscles. When they occur on the extremities, they are localized, poorly demarcated, spongy, compressible tumors with multiple bluish soft elevations resembling dilated veins. Roentgenographic examination may reveal multiple, round or linear calcifications. Unless arteriovenous communications have developed, the length or breadth of the limb is not usually increased and thrills and bruits cannot be demonstrated. The hemangioma may produce symptoms of heaviness and aching, particularly after use of the extremity. The hemangiofibroma is a rare tumor seen in infants. It occurs in the skin as a pea sized, solid, elevated, nonpurplish, red, compressible lesion which blanches on pressure. It resembles a pyogenic granuloma but the latter is a soft, ruby red, compressible, moist, crusted lesion which bleeds easily. The hemangiofibroma, which may be a fibrosed hemangioma, is easily removed with the sharp curette. Little hemorrhage is encountered.

Diffuse Hemangioma (diffuse systemic hemangioma): The lesion is rare and it usually involves the whole or the greater part of the lower extremity. It consists of multiple, distended blood sinuses

which resemble superficial thin walled veins. The extremity at birth and childhood is enlarged and discolored by increased vascularity. The measurement of the circumference of the leg increases with age. Localized, bulging, compressible, ill defined cavernous hemangiomas are present. The sinuses collapse and the circumference of the extremity decreases in size when the part is elevated. Edema may appear after increased activity. Evidences of multiple arteriovenous connections, such as lengthening of the extremity, thrills and bruits, may be present. Diffuse hemangiomas should be differentiated from varicose veins by the history of being present at birth and progressing in childhood, by the presence of numerous sinuses not connected with the saphenous systems, and by the absence of history of phlebothrombosis or venous obstruction antedating the enlargement of the leg and veins. Acute thromboses may develop in the sinuses and phleboliths may be seen in roentgenograms of the extremities.

Racemose Type of Hemangioma: It is fortunately rare. It presents a pulsating tumor of dilated, thickened tortuous arterioles and proliferating capillaries, according to Watson and McCarthy, which establish communication with surrounding normal blood vessels. They are seen in adults on the face and neck, are destructive, and appear suddenly. They may arise from a nevus flammeus. The constant arterial pulsations may erode bone or bulge into a cavity to cause fatal hemorrhage.

Lymphangiomas: Half of the lymphangiomas are located on the head and neck, 44% on the extremities and torso.

Lymphangioma Circumscriptum is uncommon, poorly defined, with superficial, grouped, scattered and thick walled shiny vesicular lesions with a verrucous crusted surface. There is a slight tendency to increase in size.

Cavernous Lymphangioma constitutes the greatest number of lymphangiomas. It is composed of dilated, lymphatic sinuses filled with lymph or a mixture of lymph and blood. It usually involves skin and subcutaneous tissues. It may occur on the face and extend into the oral cavity to involve the tongue, producing macroglossia. In the lips it may cause macrochelilia and in the cheek, macromala. It may occur on the extremities, the retroperitoneal and mesenteric regions. The majority of the cavernous lymphangiomas occur on the left side of the body. The diffuse systemic type of lymphangioma involves the whole extremity. The process is slow and it may continue for years. The skin may be normal or studded with papules. Frequently, the channels contain blood. It may clinically simulate a diffuse cavernous hemangioma but it acts like a lymphangioma. Hemangiomas, on the other hand, are not associated with papulovesicular lesions.

Cystic Hygromas: They are usually found in the neck and consist of lymphatic tissue. They are sometimes located in the axilla, in the retroperitoneal tissue, and in the inguinal region. They are somewhat compressible, thin-walled, multiloculated and transilluminate well. Transillumination is a valuable aid in differentiating a hygroma from a branchiogenic cyst. Hygromas develop from the jugular lymph sacs; the former transilluminate, the latter does not.

Treatment

The management of the various vascular nevi will not be discussed in the order of their importance but in the order in which they were presented.

Spider-Web Nevus (nevus araneus): This lesion may be destroyed by surgical diathermy with the electrodesiccating needle. A sharp pointed needle is placed in the centre of the lesion and the current turned on for a second. This is usually followed by permanent instantaneous disappearance of the nevus. Occasionally, this procedure must be carried out a second time. There is negligible scarring. The fine pointed electric cautery may also be employed. The same results may be accomplished with the electrolytic needle (electrolysis negative pole) but it is less efficient. Refrigeration with solid carbon dioxide and the injection of sclerosing solutions are unsatisfactory and the latter may be followed by conspicuous scarring in the treatment of this type of superficial lesion. Spider nevi associated with Rendu-Osler-Weber disease when they are the cause of profuse epistaxes from the nasal mucous membrane are usually treated with the electric cautery.

Senile Angioma (senile ectasia, senile vascular nevus): These lesions are best treated in the order and manner suggested for nevus araneus, but the destructive effect must include the whole lesion. The electric cautery is as efficient as the electrodesiccating needle.

Pulsating Hemangioma (pulsating spider nevus): This lesion is treated by the same methods suggested for the spider nevus. The destructive effect should be deeper. The underlying hepatic disease should be treated.

Nevus Flammeus (port wine stain, capillary nevus): Most forms of treatment leave a mottled scar (a patch quilt effect) which may be more disfiguring than the original nevus. Laymen recognize and accept the idea of a port wine mark but the effect of bad treatment invariably raises doubt as to the nature of the altered lesion. A small port wine stain may be excised and the defect covered with skin graft. Excision and grafting may be necessary when the appearance of the lesion has been made worse by ill advised treatment. Port wine stains in women can be covered satisfactorily by skillfully applied cosmetics such as covermark. It is not as successful in young children or in men because of the theatrical effect produced. The hemangiomatous excrescences can be destroyed by surgery to give a smooth surface for the esthetic application of the camouflage. Conway and Dockter have effected permanent camouflage of port wine stain of the face by the intradermal injection of insoluble pigments with the multiple electromagnetic needle (tattooing). Their method is to remove the disfiguring features of the nevus flammeus without compromising the skin. This treatment is based on the fact that in the majority of port wine stains the abnormal capillary dilatations are in the subcutis or in the lowest part of the cutis. The treatment is successful only in this type. It is not effective in the subepidermal type. The pigment is inserted into the dermal area, between it and the epidermis. The combination of pigments produce the desired tints. Lesions measuring a half foot square require about six to eight treatments. Johnson destroyed the capillaries in nevus flammeus by rubbing the skin with sterile sand paper while leaving the subcutis intact. He produced an edematous skin cushion by injecting procaine containing exadrine (1:1000 solution, 1-drop/10 cc.). He then rubbed the skin with sterile No. 2-5 sandpaper. He claimed good results with one treatment. He treated 17 patients with this method. There was no infection. The darker (dermal or subdermal) types responded better than the lighter subepidermal types.

Grenz rays, as suggested by some, are likely to be followed by undesirable radiation sequelae due to excessive exposure necessary to accomplish a fair cosmetic result. There are but few good results accomplished in the superficial types by repeated vesiculating doses of the water or air cooled Kromayer ultraviolet light.

Refrigeration with solid carbon dioxide may produce the disfiguring mottled effect mentioned above and therefore should not be used.

Occasionally a port wine mark may be so turgid and elevated as to suggest a superficial hemangioma. Failure of response to treatment of the latter suggests the diagnosis of the former.

Radiation therapy is of no value in the treatment of port wine mark. Treatment with radium is contraindicated.

Nevus Simplex of the nape of the neck (Unna's nevus): No treatment is required.

Nevus Anemicus: Treatment is not necessary because symptoms are lacking. If the lesion is conspicuous by virtue of the fact that it is on an exposed area of the body of a florid individual, covermark usually takes care of the problem.

Hemangiomas: The disappearance or involution of superficial capillary (strawberry marks) and cavernous (deep) hemangiomas may result from thrombosis of the afferent vessel. Lister reported partial or complete spontaneous involution by the fifth year of life of the superficial (capillary) hemangioma in all but one of 77 cases, but this report does not encompass hemangiomas of the mixed (superficial and deep) or cavernous (deep) type. These as a rule do not undergo involution unless small, the tendency being to increase in size. The spontaneous involution or accidental traumatic ulceration by vascular sclerosis has been used as an argument against treating these angiomas at all, or of waiting for several years before considering treatment. Not all authors agree with this high incidence of the disappearance of spontaneous involution of superficial hemangiomas. Lister made a detailed search of the literature and failed to find a single instance of the growth of a superficial hemangioma (capillary hemangioma) beyond the age of 18 months. It is extremely rare to observe a strawberry (capillary) hemangioma in an adult. Surely, all of these lesions could not have been treated, which is another argument for their spontaneous involution. It may be further argued that since cavernous hemangiomas are observed in adult life, some of them might have originally been superficial hemangiomas converted, because of trauma, etc. The number of instances in which spontaneous involution of a cavernous hemangioma occurs is relatively small and the treatment of these hemangiomas is successful if it is administered early in the first 3 months of life. Hence, it is best not to delay in the hope that spontaneous involution will occur. A good rule to follow is that most hemangiomas that grow rapidly will not disappear spontaneously. Watson and McCarthy have stated that the sensitivity of hemangiomas to irradiation with radium varies inversely with the age

of the lesion. Another argument for early treatment of cavernous hemangiomas is that sooner or later some of these lesions will develop arteriovenous connections. The therapeutic problem is then difficult and the outlook for cure is poor, to say nothing of the disabling handicap for the patient and the ever present danger of hemorrhage.

The base of every superficial hemangioma should be palpated to determine if it has an invisible submerged hemangiomatous, cavernous, deep, vascular element, as a rule much larger than the presenting obvious superficial component of the hemangioma. This type of examination is important in determining whether a lesion is superficial or deep, if it should be treated promptly, and the type of treatment to be administered. Small cavernous hemangiomas of this type may increase rapidly in size after the application of carbon dioxide snow, if the operator is ignorant of the presence of the deep element.

Meningocele occurring in the midline of the back, because of the fleshy vascular character of the lesion, must be differentiated from hemangioma.

There are certain hemangiomas, superficial and deep, which should be treated promptly because they may be situated in the orbital or periorbital regions, thus interfering with vision. They may be located at orifices of the body and interfere with function, such as on the lips in nursing, and in the perineal areas, interfering with urination and defecation. In the latter regions, they are subject to macerating, irritating effect of excreta and diapers, sometimes causing ulceration and infection. Severe hemorrhage is seldom seen following ulceration or trauma of one of these lesions. It usually can be controlled by pressure. On the other hand, injury to or ulceration of muscular, visceral, bone lesions, and those projecting into cavities may be followed by uncontrollable hemorrhage.

Most mothers express the desire to have these superficial hemangiomas removed for cosmetic reasons, in spite of the fact that they have been advised that they disappear spontaneously. Therapy under such circumstances is justified, safe and effective. The method of treatment depends on the type of nevus, the location, the age of the lesion and age of the patient, and whether infection is present. The experience of the operator often decides the type of treatment of hemangiomas.

Refrigeration with solid carbon dioxide and with liquid oxygen: This method of treatment is particularly indicated in the superficial type of hemangioma, the so-called strawberry mark. Dry ice bought at the ice cream counter is a convenient method of application. Cylinders of the solid carbon dioxide may also be made in the physician's office, by collecting carbonic acid gas in a chamois bag from a tank under pressure. They are then molded into the desired shape. The solid carbon dioxide may be applied directly to the lesion with mild, moderate or deep pressure, depending upon the degree and depth of refrigeration desired. The lesion should be well screened with a piece of blotting paper or chamois. Moderate pressure for 15 seconds will cause a bulla to form in several hours; this ruptures spontaneously, leaving an adherent crust. The purpose of the treatment is to bring about thrombosis of the vessels without deep ulceration. This treatment may be repeated when the regression of the lesion has ceased in about three weeks.

Liquid oxygen has been used especially by Kile and Wel[illegible] It can be obtained in one liter (1000 cc.) containers. It is inexpensive and safe, if properly han[illegible]d. Since it is readily combustible, contact with fire must be avoided. It has a critical temperature of —119° C. at 50 atmospheres of pressure. Applications are made by using cotton applicators. The tip varies in size and shape to conform to the lesion. The applicator is dipped into the oxygen and applied with varying degrees of pressure depending upon the size of the lesion. The length of time varies from 10 to 20 seconds. Moderate pain is present. The fact that most of the pain occurs after the treatment makes it advantageous in the treatment of children. A bulla occurs at the site of application. This is followed by a crust. The interval between treatments is the same as for that when solid carbon dioxide is used. The cryocautery has been used with less success. If these modalities are properly and carefully applied, scarring is minimal and, in the superficial lesions, negligible. One must be careful in using solid carbon dioxide or liquid oxygen around the eyes for fear of accidentally injuring the eyes by detached pieces of snow or droplets of liquid oxygen.

Refrigeration therapy is usually unsatisfactory in the treatment of cavernous hemangiomas because of the inability of reaching the depth of the lesions by freezing. It may be used for the remaining islands of superficial hemangiomas following treatment of the cavernous type with sclerosing solutions. It is of no value in the treatment of the port wine mark, because this form of treatment produces a patch quilt effect which is more disfiguring and more difficult for the patient to explain

than the port wine mark which is familiar to most people. One of the great advantages of refrigeration therapy is the fact that it is rarely followed by keloid formation.

Injection of sclerosing solutions: This form of treatment is simple, effective and relatively harmless, having a special place in the treatment of cavernous hemangiomas. The excellent results published by Andrews and Kelly and more recently by Crawford indicate that it compares favorably with other methods of treatment. The sclerosing solution is injected into those regions in which it would be somewhat hazardous to use radium, such as the eyelids or genitals. Crawford lists the following solutions according to their relative merit: 1. 30% invert sugar solution with the addition of 10% sodium chloride and 1% phenylethyl alcohol; 2. monoethanolamine oleate 5% dilution with 2% benzyl alcohol; 3. sodium morrhuate solution 5 to 10%; 4. sodium citrate 30%; 5. quinine and urethane 50%; 6. boiling water.

Quinine and urethane is occasionally followed by dermatitis medicamentosa, much less frequently in infants than adults, sodium morrhuate by systemic reactions and sodium citrate by severe pain. A 26 gauge needle attached to a 0.5 cc. tuberculin syringe is introduced directly into the center of the hemangioma. The amount of solution injected varies from 0.2 cc. to 3 cc. depending upon the size of the lesion. If hemorrhage is anticipated, the needle may be inserted into the normal skin at the periphery of the lesion. The solution is injected in small amounts (0.1 cc.) at various points equally and diffusely distributed throughout the lesion. If possible, blanching and coalescence of instillations should be avoided. Compression is applied immediately after injection and maintained for several minutes. It is wise to make the first dose a test dose, giving 0.05 cc. to anticipate possible allergic sensitivity. If the tumor is growing rapidly the lesion should be treated at weekly intervals. If not, several weeks may elapse. This form of therapy is not indicated in superficial hemangiomas because the vessels are rather small and the connective tissue stroma profuse. It may be tried with less promise of success in the treatment of cavernous hemangiolymphangiomas and cavernous lymphangiomas and hygromas, also diffuse, systemic hemangiomas and occasionally racemose hemangiomas. There is considerable pain as the sclerosing solution is injected into the tissues. It may last five minutes and a dull pain may last for several hours. The hemangioma treated by this method may enlarge to twice its size within 10 or 15 minutes, and increase to four times the original size during the next 24 hours. The reaction takes about a week to subside. The location of the tumor is important because poor results and failures occur with greater frequency when the lesions are located on the face or in the mouth. As it is with all modalities, the sooner the lesion is treated, the more rapid will be its response to therapy. It is important to keep the solution from being deposited too superficially because ulceration, sloughing and keloid may follow. In treating the cavernous hemangioma with superficial and deep element, treatment is to be directed to the deep portion; the superficial element will disappear as the deep portion undergoes sclerosis. Sclerosing solutions are most effective in the treatment of the soft compressible hemangiomas of the cavernous type.

Radiation therapy: This form of therapy may be used with varying degrees of success in the different types of hemangiomata. MacKee and Cipollaro state that "X-rays and gamma rays of radium are capable of curing the superficial hemangioma, but the effect of the beta rays of radium is so superior that X-rays and gamma rays are seldom used. The results of beta ray therapy in nevus vasculosus are so striking, so perfect, that they may be placed among the most notable achievements of radium therapy in the treatment of cutaneous affections." Radiation therapy is indicated in children because of its ease of application and the absence of pain. Its best indication is the cavernous hemangioma, where gamma radiation with radium, when properly used, is effective and safe, offering good therapeutic and cosmetic results. The intervals between treatments should be gauged by the rapidity of regression of the tumor and subsequent treatment should not be administered until regression has become stationary. It is important that radiation therapy be instituted before the lesion is three months old. Seldom do cavernous hemangiomas disappear spontaneously; therefore, they should be treated early and at a time when they are most radiosensitive. Watson and McCarthy have stated that the radiosensitivity of hemangiomas varies in inverse proportion to the age of the patient. If this type of lesion is not treated early, it may later develop arteriovenous connections, which is extremely difficult to eradicate. High voltage roentgen ray therapy (filtered) has been used with success for cavernous hemangiomas of the skin but especially is it indicated in deep-seated hemangiomas, such as those of the vertebrae and liver. Both radium and roentgen rays should be administered with caution in the following locations, at all times knowing the half value layer: hairy

parts, such as the scalp, eyebrows and eyelids, where permanent conspicuous alopecia may occur; mammary glands and genitals, because of subsequent disfiguring and functional atrophy of these organs; the epiphyses of long bones, facial bones, digits, because of the premature ossification of the centers of growth, causing in some instances shortening of a limb, or facial hemiatrophy; on the vermilion border of the lips and the labia, because these parts are susceptible to the future development of epithelioma, and in the former location because of possible effect on dentition; the orbital and periorbital regions, because of danger of secondary changes in the crystalline lens. It is to be remembered, however, that Andrews reported a case where a cataract occurred in a child who had a periorbital hemangioma in spite of the fact that this child had not received roentgen ray therapy. There are some who rightly believe that radiation therapy is not prone to produce cataract unless the dose is excessive, because the human eye is fairly resistant to radiation therapy. Surgical cure may be more successfully accomplished following injections with sclerosing solutions which render the hemangioma smaller, less bulky and easier to excise. Radiation therapy is often more successful after sclerosing solutions have been used. Refrigeration should not precede or follow radiation therapy.

Radium treatments are time-consuming and require expert care of a physician with long experience in the use of radium. Since a large amount of radium is required to treat a number of these babies simultaneously in an active outpatient department, many hospitals can ill afford the expense. Sclerosing solutions have become popular because of this fact.

Radiation therapy is inadvisable for extensive lesions. The great difficulty in the treatment of hemangiomas with radiation is the fact that those physicians who use it try to "whittle" the lesion from the top downward instead of using radium at a distance, so that it will affect the deeper parts of the hemangioma and thus spare the skin. It is good treatment for the superficial hemangioma but is not as safe in the hands of those who are not highly trained in the use of radium, as refrigeration with solid carbon dioxide. Radiation is of some value in the cavernous type of hemangiolymphangioma and it has little effect on the other forms of lymphangiomata.

Various types of roentgen ray radiation have been used, according to Pfahler: high voltage and high filtration, low voltage and moderate filtration, and contact therapy and little filtration.

I have used the electric cautery and surgical diathermy in the treatment of small superficial hemangiomas but it is not as fine a treatment as refrigeration because of the danger of the development of keloids in the former. Surgical excision is seldom necessary unless a cavernous hemangioma is increasing in size in spite of treatment. A small lesion may be excised with good cosmetic result The surgical treatment of hemangiomas is performed in stages and is likely to be followed by keloid formation.

The treatment of diffuse hemangiomas is difficult, painstaking and not satisfactory. The injection of sclerosing solutions has limitations because it is not feasible to sclerose all the sinuses in this type of hemangioma as they continue to evolve. When diffuse cavernous hemangiomas occur on the lower extremities, ligation of the saphenous veins and retrograde injection of sclerosing solutions may be employed with partial success, and the use of compression bandages or heavy elastic stockings also may be useful in preventing the heaviness of the limb, pain, swelling and edema of which these patients complain.

Lymphangiomas: Gant treated a superficial type of lymphangioma circumscriptum successfully by refrigeration with solid carbon dioxide pencils with good therapeutic and cosmetic results. Surgical excision affords the best prognosis in the treatment of lymphangiomas. Surgical excision is likely to be followed by keloid. This group of vascular nevi are resistant to radiation therapy. In the treatment of diffuse systemic lymphangiomas which affect the entire extremity, high voltage roentgen therapy may be tried. Sclerosing solutions are of little value in the treatment of lymphangioma with the exception of the cystic hygroma. The mortality rate in hygromas is high.

Experience has taught us that no one method can be applied in the treatment of all vascular nevi, or in the treatment of a single type. By and large, each lesion is a law unto itself with the possible exception of the superficial hemangioma.

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430 Humphrey St.
New Haven 11, Conn.
(Died Sept. 1, 1949)

Dr. John William Amesse (Emeritus Member)
1675 Kearney St.
Denver 7, Colo.
(Died Aug. 21, 1949)

Dr. Charles A. Aldrich
115½ 1st Ave., S.W.
Rochester, Minn.
(Died Oct. 6, 1949)

Dr. Paul E. Belknap
726 Mills Bldg.
Topeka, Kan.
(Died Aug. 29, 1949)

Dr. Jose Bonaba
Maldonado 1169
Montevideo, Uruguay
(Died Aug. 16, 1949)

Dr. Charles J. Cole
7926 Park Ave.
Elkins Park, Pa.
(Died June 22, 1949)

Dr. Thomas J. Donovan
5101 Fannin St.
Houston 4, Texas
(Died March 3, 1949)

Dr. Pedro de Elizalde
Vicente Lopez 1878
Buenos Aires, Argentina

Dr. R. S. Friedley (Emeritus Member)
218 Twin Oaks Rd.
Akron 3, Ohio
(Died Aug. 1, 1948)

Dr. George C. Glass
576 Farmington Ave.
Hartford 5, Conn.
(Died July 5, 1949)

Dr. Hal R. Hoobler
Franklin Bldg.
Oakland 12, Calif.
(Died June 20, 1949)

Dr. Elmer G. Horton (Emeritus Member)
285 E. Lane Ave.
Columbus 1, Ohio
(Died May 1949)

Dr. George D. Lyman
384 Post St.
San Francisco 8, Calif.
(Died July 1949)

Dr. James H. McKee (Emeritus Member)
372 W. Johnson St., C 5
Philadelphia 44, Pa.
(Died March 24, 1949)

Dr. Silas S. Snider
2017 W. 95th St.
Chicago 43, Ill.
(Died June 15, 1949)

Dr. Henry W. Titus
421 Huguenot St.
New Rochelle, N.Y.
(Died March 17, 1949)

Pediatrics

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SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

AN OPEN FORUM

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

COMMUNICATIONS FROM DRS. H. G. PONCHER, JOHN K. GLEN AND ALLAN M. BUTLER

DEAR DR. PARK:

The eloquent statement on the status of Negro medical care and education in the United States by the eminent anatomist, Dr. W. Montague Cobb (Brown America's Medical Diaspora: A Paradox of Democracy, in The Pediatrician and The Public, PEDIATRICS 3:854, 1949) requires the attention of all physicians interested in the distribution of medical care. Although pediatricians cannot begin to assume responsibility for this entire problem, it is possible to demonstrate leadership in the same manner in which the Academy study of infant and child health services provided leadership to the profession and the public.

We refer specifically to an extension of training facilities in pediatrics for Negro physicians. Certainly 15 certified Negro pediatricians in a country with 14,000,000 Negro people represents a serious discrepancy in the distribution of training facilities. Admittedly most of the problem has its origin in the distribution of training facilities for undergraduate students and the basic problems responsible for this situation. However, we have observed—as has Dr. Cobb—that many Negro physicians desiring training in pediatrics (as well as other specialties) are discouraged from applying for training because of what seems to be a dearth of positions open to them. It has been our impression, however, that many centers would consider Negroes for training appointments if qualified applicants applied. Would it not be advisable, therefore, for the American Board of Pediatrics to circularize the approved training centers in pediatrics in order to establish a roster of those centers which would consider Negro applicants for training positions?

We reiterate that this is not proposed as a basic solution to a serious problem, but rather as palliative therapy for an immediate situation which merits action.

In the interest of attempting to obtain a consensus on this proposal, we are sending copies of this letter to Dr. John McK. Mitchell, Executive Secretary of the American Board of Pediatrics and to Dr. Warren R. Sisson, President of the American Academy of Pediatrics.

(Signed) H. G. PONCHER, M.D.
Chicago

DEAR DR. HARPER:

I appreciate your invitation to criticise the article of Dr. R. S. Illingworth which appeared in the October issue of PEDIATRICS. I know many others who would have been equally happy to criticise the article and of them I beg pardon for grasping the opportunity myself. Unquestionably, many others could do better than I.

It shall not be my object to write in derogation of the British people, the British government, the British medical profession or the British National Health Service. It is, rather, my purpose to comment upon Dr. Illingworth's article with the hope that those in America who have not already done so will see the hopelessness of socialism. Inasmuch as Dr. Illingworth's paper has appeared in this American journal, nothing less than free comment upon it by American pediatricians is to be expected. Be it said to Dr. Illingworth's credit that he did not suggest that a socialist government, or a national health service patterned in British fashion, should be adopted by us or any other nation.

It is, however, advocated by too many in America that we establish a system of state medicine here, originally in the form of compulsory sickness insurance, federal support of medical education, federal funds for school health, etc. This advocacy comes from some quarters of a desire to do good for those who need help. It comes from other quarters as a means of controlling our economy and politics. Yet again it comes from those thoughtless persons who are influenced by constant exposure to such articles as Dr. Illingworth's to think it possible to get good medical service free. It is, therefore, necessary that we deal with the British system, and reports upon it, in a thoroughly rigorous manner, for many are convinced that compulsory sickness insurance is a very important one of the many ways in which America can be made as socialistic as is Britain.

Thoughtful persons reading Dr. Illingworth's paper must be amazed at its philosophy, its contradictions, its doubts, its economic hopelessness. Dr. Illingworth appears to be a good essayist and has recorded his observations well. I gained the impression that he was defending the British National Health Service in some such manner as a loyal husband would defend his habitually drunken wife: because the situation is *his*. He gives many justifications for the service, but the weight of his argument is against it.

Individuals (and we must remember that the individual is the only human entity) living in groups such as nations form their personal philosophy around the answers to two simple questions: 1. What do I want? 2. If I may have one of two desirable things, which will I choose? In many instances the answers to these questions are forced upon individuals and nations by circumstances beyond their control. In arid lands people want water; in war-torn lands they want peace; in bankrupt lands they want things wealth can bring. However, the fundamental consideration is that individuals are motivated, not by

needs as seen for them by others, but by desires as felt by them. Even in the individual the recognition of a need does not lead to its fulfillment until the need is activated by desire. Human beings are made that way. Once an individual wants or desires something he is motivated to get it. But the means chosen by an individual, or a nation, to attain his or its objective depends upon the intelligence, the moral fiber and the spiritual understanding possessed by the one who desires.

It is not strange that in Great Britain, war-torn, weary and bankrupt, the philosophy should differ from ours. The question we must ask ourselves is not, "Were the British wrong in the course they chose?" but, "Would we be right in following a similar course?"

That Britain's health was bad at war's end goes without saying. At the outset Dr. Illingworth says, "There is no doubt at all that the country wanted comprehensive health service." This is given under the title "The Need for a Comprehensive Health Service." Most of us in America realize that there is a very practical difference between what we want and what we can afford and/or need. But elections are apt to be won upon a basis of what people want. The British wanted a National Health Service. That fact is significant for us because we must determine what we want. All sincere, honest persons in America want all our citizens to have good medical care. Some would have us vote in a system like the British National Health Service because its advocates promise that it will attain the desired objectives. Others (and these include me) would help vote in such a system if we could be convinced that it did not involve a choice: health service or freedom. According to Dr. Illingworth, the British had that choice. It was up to them to decide which of two things they most desired. Dr. Illingworth—and, I suspect, most other thinking Britons—are wondering if they made a wise choice, for they put health service first—above freedom. He states: "All doctors, quite naturally, fear loss of freedom by an increase in the powers of the Boards and of the Minister. The danger is a real one. The Boards have a great deal of power. *One can only hope** that the Boards, the Central Advisory Committee, the professional organisations and public opinion will prevent encroachments on the freedom of the doctor *unless it is quite definitely in the interests of the community.*"*†

Let me ask you American readers, mostly physicians, to reread the above statement and answer this: Do you want your only hope of freedom to rest upon the discretion of a gang of Boards and Committees of a socialist government? We should remember that the unwillingness of the founders of the American Republic to gamble so loosely with freedom produced our Constitution limiting our government in such a way as to prevent the dependency of our liberties upon government boards born of political expediency. We must preserve our Constitution intact!

If doctors are to lose their freedom "in the interests of the community," as Dr. Illingworth implies they would be willing to do, why would not other groups lose their freedom too "in the interests of the community": plumbers, bakers, all trades, professions and businesses; *all patients?* The loss of freedom "in the interests of the com-

* Italics mine.

† One should note with care how collective nouns such as community, people, peoples, groups, classes, common man, labor, capitalists, Jews, Gentiles, Protestants, Catholics, the rich, the poor, etc., are used cleverly by collectivists to efface the individual. Such effacement is the essence of communism and socialism and the antithesis of the American ideal of individual freedom and dignity.

munity" is, to my way of thinking, communism pure and simple. If we are to lose our freedom for a health service we shall then possibly have some healthy slaves—but who wants to be one? Or, who among us think it is wise to risk being one?

Two great Americans long ago expressed themselves on this choice between health and freedom. Emerson wrote:

"For what avail the plough or sail,
or land or life, if freedom fail?"

and Patrick Henry was not engaging in histrionicism when he wrote,

"I know not what course others may take but as for me, give me liberty or give me death."

I have little doubt that today, in spite of those in high places who would have us choose a health service at the risk of freedom, the American individual will shape his philosophy to a choice of freedom before a government health service. I trust that we in America believe that with freedom we may, in time, solve our health problems; that a government health service is not worth even a risk to freedom.

Neither philosophy nor economics seem easily disposed of in a few words. I wish it were so. As distressing, almost, as is the British choice of health service before freedom is their haziness in economics. I am of necessity an economiser and therefore am interested in economics. I know ordinary arithmetic and my Scot and Dutch forebears taught me that "zero, take away one" would leave me in the hole. Dr. Illingworth honestly poses many astonishing inconsistencies in economic thinking. However, he seems less confused than is the system. Without quoting his exact words, he says that all possible medical services are provided by the Ministry free of charge to every man, woman and child. He says the majority of the people have no idea of how the Health Service is being financed. *He* knows for he says one tenth is paid by the National Insurance contributions and nine tenths by general taxation. To quote, "Everyone pays for it and pays a lot, but it does give security—security against the devastating effect of illness on the purse."

Perhaps I don't know what the above means in Britain, but I know what it would mean and does in America. We must ask, "Wherein does the security lie?" If all the money His Majesty's Socialist Government has to spend on everything were put in a barrel, stirred with a stick, then meted out for the various purposes of the government (including the Health Service) there would be a sprinkling of American dollars in each allotment. Perhaps we Americans are Shylocks to care where our money goes and for what—we are unfortunate that way. I, as do other American physicians, work rather long hours for my money. I pay what I consider pretty high taxes. So I am interested in where my "effort" goes (a more genteel way of putting it). Some of my money out of our stirred barrel goes to Britain to get stirred in her barrel. Then some of my effort is going to help pay hard-working British physicians to take care of British laymen who want to and do work little more than half the hours I put in. It makes me wonder about the value of "security." Security, like medical service, isn't free—nor can it be made free. Somebody pays for it! Except on an actuarial basis people can't afford collectively a thing which they can't afford individually. In our country we have believed nothing is free. We have contended that things are obtained at the price of brains, brawn and/or financial risk. We have, as yet, no reason to change our faith. We believe that a health service which is not self-supporting is not secure.

Dr. Illingworth shows that with 4,000 on his list, at $3.25 per head, a doctor can gross $13,000 ($9,100 since the devaluation of the pound-sterling). Of course, overhead must be paid out of this—and taxes. He says for the Service this is fair pay. Then he says no doctor should be allowed to have 4,000 on his list because he can't possibly take care of them. It occurs to us here to ask: "Who will reduce the lists? To what number will they be reduced? It seems a British physician can get along only if he does so much work he can't possibly accomplish it! How will he live if he does less?" Americans will view such contradictions as patently fuzzy thinking.

Economics and freedom (or loss of it) can be most intimately intertwined. This admixture we must take seriously at this juncture as Dr. Illingworth swallows his conscience with this: "Practitioners have to a considerable extent lost the freedom of settling in a practice of their choosing. They cannot settle in a practice where they wish unless there is a need for a doctor in that area, or unless they stay outside the service altogether, as they can if they so desire. . . . The doctor has clearly lost freedom in this important matter. . . . It can hardly be denied that this 'direction' of doctors is to the advantage of the community and is inevitable to some degree if the government is to fulfill its pledge to provide a reasonable standard of medical service in all parts of the country." This insidious loss of freedom is the more dangerous because to the unthinking it seems so reasonable. Dr. Illingworth seems not to realize that "planners" usually take away freedoms little by little and that the next step is always justified in some rational way before it is taken. The steps are always made to accomplish some good purpose. The significance of this for us is that similar schemes are actually planned for us in America. The Committee for the Improvement of Child Health of the American Academy of Pediatrics, in its original recommendation, actually suggested government subsidy to "direct" doctors to areas of need in America. This, of course, is not to be confused with the thoroughly American, so-called Kansas Plan. Economic bludgeoning is the usual step by socialist governments before resorting to physical liquidation for nonconformity. Economic means of coercion are apt to become more burdensome to the planners than simple annihilation. Please to remember that these steps have been taken repeatedly in other countries within the past two decades!

Another Illingworth profundity is quoted here: "Some patients have undoubtedly abused the service and demand bottles of medicine or applicances which are unnecessary. It is difficult to see how such abuse, which depends on the character of the individual, can be prevented." I tear my hair as I consider this one! But, at the same time, I say "Bully" for Dr. Illingworth and his fellow Britons who can't see what can be done! It may mean they don't intend to give up their freedom, and I desperately hope they won't. I think the British should have peeked in and seen what some of their neighbors did about that problem. 1. They set up a limited "supply-table" and the bottle of medicine and appliances were simply "out of stock." 2. An "extra compensation" was given to the doctor who reported such a troublesome character for sentence to a few years of forced labor. 3. The doctors were hauled before Boards and disciplined for not conserving "the Fund." Dr. Illingworth admits that the third method has been used in Britain.

The greatest consideration, I think, was left by Dr. Illingworth to the last of his paper: "It seems inevitable that the cost of the Service will continue to increase. Taxation is already excessive, and one of the highest in the world, and it is difficult to see how it can be further increased." All right, then what happens to the Health Service? This, of course, is of no moment because the Health Service per se is a nonentity. The pathetic con-

sideration is: What happens to the health of the individual citizen where the costs inevitably rise and taxes can rise no more? Further, what happens to all the other interests of the nation which have been bound inextricably by "community interest" with the Health Service? I suspect that the British have peeked in for a look at their neighbors' solutions to this problem and I can imagine they are not happy with what they saw: some hand-writing on a wall to the effect that, "Socialism can succeed only by the use of brute force."

Dr. Illingworth's article may well be taken as a guide to the things we should not do in America.

In his last short paragraph, Dr. Illingworth leaves a loophole, "It is far too soon to make a proper evaluation of the Health Act. The opinions expressed are those of the writer. He is fully aware that in a year or two those opinions may have completely changed." The questions which we in America would ask in this regard are: Suppose he does change his opinion in a year or two, (1) what will he do about it? By what means will he live? (2) Can he, as a writer, express the opinions of the writer?

Much in Dr. Illingworth's article seems good. Unquestionably the objectives are good. But throughout my reading of his exposition, I was reminded of the sumptuous meals given to condemned men on the eve of execution. Undoubtedly, as a free man, I could go for the menu offered; but, not free, I am sure I would yearn for a plainer fare.

(Signed) JOHN K. GLEN, M.D.
Houston, Texas

DEAR DR. HARPER:

You are to be congratulated on having obtained and published Dr. Illingworth's appraisal of the first year of the British National Health Service. Such an objective and unprejudiced presentation is much needed here where so much of the comment, particularly, I regret to admit, of our medical profession, gives a prejudiced selection of results and thus a distorted evaluation of the total Service. If only we could view the matter dispassionately, what a gold mine of information would be available for us to explore by critical study and process to our needs.

Dr. Illingworth comments on one point that deserves emphasis because it is so generally ignored in this country, namely, the difficulties resulting from a medical service plan making fee-for-service payments to individual practitioners, in this case to dentists. This evidence adds one more proof of the unsuitability of this method of paying doctors under a voluntary or legislated health service where the recipient of the service does not pay the bill. That the British were more aware of this than we are is evidenced by their not using fee-for-service in paying the family physicians whereas this method is generally advocated by physicians here. That we do so is odd because this type of remuneration has so many disadvantages. It tends to put the wrong emphasis on the role of the family physician, who should be the backbone of any medical service and who should be concerned as much with the health as with the sickness of his patients. His income, therefore, should not be dependent on fees for seeing patients when ill and should not be jeopardized by his patients' being well. Moreover, not infrequently patients should be referred to consultants and specialists by the family physician. The remuneration of the family physician should not be affected adversely by the readiness with which he fulfills this important role. It is, of course, only physicians with poor medical

ethics who let their judgment of need for medical care be influenced by receiving a fee for the service given. But insofar as some may, the contributions paid into the Service Plan tend to be drained off in paying for unneeded or inadequate medical care. In either instance the conscientious doctor and the patient suffer by underpayment and poor medicine, respectively. This method of paying also entails a burdensome amount of paper work with each service rendered. This work demands more bureaucratic personnel and increases costs of administration, again reducing physician remuneration or service to the public.

This appears to be just what happened in all pre-payment plans that have fee-for-service as the basic method of payment. Isn't it puzzling that the AMA has endorsed plans that do this and has opposed the inception of all the medical service plans that have avoided this error by paying physicians on a per capita or salary basis? And isn't it odd that there is an antagonism to these two alternative methods of paying doctors? By them the disadvantages mentioned above are avoided without removing the healthy competitive stimulus of satisfying patients or professional peers.

Perhaps, until the fallacy of fee-for-service payments under medical service plans are more generally recognized by doctors and public, neither voluntary nor legislated plans should be extended rapidly. Indeed, one wonders if the profession does not appreciate the incompatibility of third party (Blue Shield, for example) payment of medical costs and of fees for each service rendered by individual practitioners, and if its lack of enthusiasm for insurance medical services is not based on its altogether unjustified fear that other methods of payment may lower doctors' incomes. But now that the profession advocates the extension of the insurance principle in meeting the costs of health and medical care, this fear does not justify the perpetuation of a method of paying physicians that jeopardizes their proper remuneration and the quality of their service.

(Signed) ALLAN M. BUTLER, M.D.
Boston

TRENDS

By JOHN P. HUBBARD, M.D., *Contributing Editor*

This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

STATE REPORTS: PROGRESS IN WISCONSIN

AS OF present date the states listed below have published reports of the study of child health services. Most of the other states are known to have reports in various stages of preparation.

Alabama	Massachusetts	Oregon
Connecticut	Mississippi	Rhode Island
Florida	Missouri	South Dakota
Georgia	New Jersey	Washington
Idaho	New Mexico	Wisconsin
Iowa	New York	Wyoming
Kentucky	North Carolina	District of Columbia
Louisiana	Ohio	

It is timely to note some of the steps being taken to activate the recommendations of these state reports. The following communication from Dr. Tenney, State Chairman for Wisconsin, is one example of significant progress being made at the state level:

DEAR DR. HUBBARD:

As a first step in activating the findings and recommendations of the Wisconsin Study of Child Health Services, the committee decided to inaugurate the plan of "roving residents." The theory and scope of the project is well set forth in a letter which Mr. Roy T. Ragatz, assistant secretary of the State Medical Society, sent to the officers of the county societies selected as trial areas. He states:

"The Committee on Maternal and Child Health of the State Medical Society, in cooperation with the State Board of Health and the Pediatric Departments of our two medical schools, has been working on a program which we feel will be of great service to your members if properly introduced and adequately supervised.

"It has been proposed that a carefully selected number of pediatric residents be made available to selected county medical societies for a short period of time this spring to work with individual members who have special pediatric problems they wish discussed. The plan is to supply this service *only upon the invitation of the county medical society* and it is to be set up in such a way that there will be no conflict with private practice or the normal channels of consultation.

"The plan briefly is this: one of three carefully selected residents from Children's Hospital, Milwaukee, who is about to complete his training, will spend a short time in Northern Wisconsin this spring, working under the direct supervision of Dr. Henry Sincock, Superior, and Dr. C. J. Smiles, Ashland, but making himself available to any physician in your county society for assistance in pediatric problems. This would not be a

general res dency service, and the young man serving your members would be restricted to certain specific activities which would be agreed upon by your society and the sponsors in advance of his service to your membership.

"The tentative plan would be to have this young man (who is already committed to practice in another city far away from the Superior-Ashland area) come to Northern Wisconsin for a month. He would spend approximately three weeks in Superior and one week in Ashland, or two weeks in Superior and one week in Ashland, and a fourth week in another city, possibly Ladysmith.

"The purpose of this service is to provide a form of education which is two-way: It is felt that the individual practitioner can derive help and information from the resident on the basis of his recent training, and the resident, in turn, will be confronted with a variety of situations which will broaden his education and give him a better understanding of pediatric problems confronting the individual physician outside of the teaching areas of the state.

"We hope that your society will avail itself of the opportunity for this service and, inasmuch as it is a carefully controlled experiment, to ascertain its values to both the physicians and the residents involved. We will welcome your help in seeing that the program attains its objectives of mutual benefit.

"Drs. Sincock of Superior and Smiles of Ashland have been asked to assume direct supervisory responsibility of the program. We would suggest that this matter be discussed with them, so that there will be no misunderstandings on the part of your members concerning this proferred service."

At the conclusion of the project it was decided that we should make a critical appraisal of the service rather than simply assume that we were correct in our unanimous opinion that such a service would be of benefit to the physicians of the state. Therefore a questionnaire was sent to every physician in the area served asking for frank "off the record" opinions. The replies, we feel, justify our conviction that the project was worth while and should be repeated in various parts of the state each year.

It is most gratifying to see this project receive the endorsement and active cooperation of so many agencies, namely, the Academy, the State Medical Society, the State Board of Health (Bureau of Maternal and Child Health), and the County Medical Societies. But most of all it is gratifying to note that the physicians of the state feel that it will help them give better medical care to the children of the state.

(Signed) H. KENT TENNEY, JR., M.D.
Madison, Wis.

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

MYRON E. WEGMAN, M.D., *Contributing Editor*

RESOLUTIONS OF THE AMERICAN PUBLIC HEALTH ASSOCIATION

AT THE Annual Meeting of the American Public Health Association held in New York City on Oct. 24 to 28, 1949, a series of resolutions were passed, many of which concern child health. Such resolutions are customarily presented by one of the several sections of the Association after consideration by the membership of the section and those particularly interested in the specific problems. Subsequently, the content of each resolution is reviewed carefully by the Governing Council of the Association, a widely representative body, and the resolutions in which there is general concurrence are passed and become official statements.

The following resolutions are selected from those passed at the recent Annual Meeting as being of particular interest to pediatricians:

RESOLUTION ON CHILD HEALTH SERVICES

WHEREAS, the Study of Child Health Services of the American Academy of Pediatrics has shown that many children, especially in rural areas, still lack adequate public health services, and

WHEREAS, present laws provide limited amounts of federal funds, and

WHEREAS, the Association of State and Territorial Health Officers recently indicated the need for additional funds, be it

RESOLVED, that the American Public Health Association recommends that all states and territories increase their respective appropriations in order to furnish to the people those services shown to be lacking by the Study of the American Academy of Pediatrics.

RESOLUTION ON THE MID-CENTURY WHITE HOUSE CONFERENCE

WHEREAS, the series of White House Conferences on Children and Youth have added much to the health, happiness, and well being of children, and

WHEREAS, the theme of the Conference, development in children of the mental, emotional, and social qualities essential to happiness and responsible citizenship, is a concern of family, school, church, community, and all social and health agencies, be it

RESOLVED, that the American Public Health Association calls for wide support for this Conference and recommends that all official and voluntary health agencies, national and local, take the leadership in achieving the desired goal.

RESOLUTION ON THE CONFIDENTIAL NATURE OF BIRTH RECORDS

WHEREAS, physicians attending at births are required by the respective state laws to complete and file a certificate of birth and have an interest in seeing that none of the data contained therein is used to the detriment or embarrassment of the child and family concerned; therefore be it

RESOLVED, that the American Public Health Association commends the efforts of the American Association of Registration Executives, the Council on Vital Records and Statistics, the Children's Bureau and the National Office of Vital Statistics to formulate a policy maintaining the confidential nature of birth records, and be it further

RESOLVED, that the American Public Health Association urge state legislatures and governing bodies of countries represented by the membership of this Association and their registration officials to study carefully the recommendations made and wherever possible to put them into effect by enactment into law or by administrative regulation. It especially urges that the right of inspection of birth records be restricted to the registrant, if of legal age, his parents, guardian or their legal representative, health and official agencies on the approval of the official custodian of vital records or on court order.

RESOLUTION ON OLEOMARGARINE

WHEREAS, scientific evidence has shown that fortified oleomargarine supplies the food factors usually expected of butter, and

WHEREAS, present federal and state taxes on oleomargarine seriously raise the retail price of this commodity, thus violating the principle that government should facilitate rather than hinder the provision of a satisfactory diet for all the people, and

WHEREAS, there is need for immediate consideration of this question by the next Congress, be it therefore

RESOLVED that the American Public Health Association condemns specific taxes on oleomargarine, reaffirms its stand taken on this problem in 1947, and respectfully petitions the Congress and the various state legislatures to repeal these taxes.

RESOLUTION ON CHEMICAL ADULTERATION OF FOODS

WHEREAS, there is an increasing use of chemical substances and other new ingredients artificially introduced in foods in their production or processing, and since many of these substances introduced purposely or accidentally may either directly or indirectly affect the nutritive value of the foods which contain them, and

WHEREAS, the Food and Drug Administration of the Federal Security Agency is qualified by experience and is authorized by the Congress to protect the interests of consumers in regulating the composition and the labeling of many articles of food, therefore be it

RESOLVED that the American Public Health Association recommend to Congress that it amend the existing Food, Drug and Cosmetic Act to prevent the incorporation into foods of chemicals or other new ingredients before they have been reviewed and approved by the Food and Drug Administration, and

BE IT FURTHER RESOLVED that since the Food, Drug and Cosmetic Act applies only to articles shipped in interstate commerce, it is recommended by the American Public Health Association that the official organization of state and territorial health officers be informed of the desirability of the enactment of similar legislation by states.

RESOLUTION ON SURVEYS OF NUTRITIONAL STATUS

WHEREAS, medical appraisal of nutritional status are of great importance in the field of public health, particularly with reference to such conditions as anemia, dental caries, body weight, enlarged thyroid glands and other physical means of identifying malnutrition, and

WHEREAS, it is commonly known that many surveys are being carried on independently by various health groups throughout the country, be it

RESOLVED, that the United States Public Health Service and Children's Bureau compile complete and current information on the extent of these surveys in order that they may assist local and state health departments working in cooperation with medical schools and schools of public health, for the purpose of establishing suitable criteria that can be used in the development and measurement of nutrition programs.

INTERNATIONAL NEWS AND REPORTS

NEWS FROM SCOTLAND

RICHARD W. B. ELLIS, M.D., *Corresponding Editor*

Since the National Health Service was officially born on July 5, 1948, and is already well past its first birthday, it would seem a suitable time to review the progress of this peculiar infant (or rather infants, since the Service in Scotland is administered under a different Act from that in England and Wales, and the Secretary of State for Scotland serves as midwife cum wet-nurse to the Scottish infant, whilst the Minister of Health disciplines its English cousin). It must be said at once that neither baby is yet walking securely and that both are having severe teething troubles. The first year of life has been marked by periods of vocal diarrhoea and administrative constipation, whilst the stigmata of prematurity are still painfully obvious. This is not surprising, since the scheme was begotten on the medical profession under protest, labour was induced and extraction was finally effected against considerable resistance by the maternal passages. Fortunately, the Scottish infant was less roughly handled by the midwife and started life in a state of blue rather than white asphyxia. By many, the baby was regarded as unwanted from the first and many attempts were made to abort or strangle it. During the past year, however, there has been a growing realization that the child has come to stay, and a consequent determination to make the best rather than the worst of it.

With the recent publication of establishments, it is seen that pediatrics has in fact been given much greater recognition than would have been conceivable 10 years ago. The immediate difficulty is now likely to be the filling of posts with fully-trained pediatric consultants, who are in short supply owing to the disruption of pediatric training during the war years having been much greater than in any other specialty. This difficulty, however, may be regarded as purely temporary, since there has been a notable increase since the war in the number of graduates wishing to train in pediatrics. In spite of an increased number of consultants and consulting centres, however, there is every indication that the great proportion of domiciliary pediatrics will remain in the hands of the general practitioner as at present. This alone would make it essential for pediatrics to occupy an increasingly important place in the undergraduate curriculum and in the postgraduate refresher courses for general practitioners. In Scotland, owing to the larger proportion of hospital beds which are used for teaching purposes, it is probable that a higher proprotion of consultant appointments will carry teaching duties than is at present the case in England.

The practical difficulties facing the new service are many and critics have been apt to blame the service for deficiencies which are primarily the result of the present economic situation, or the direct result of factors quite unrelated to nationalisation. Amongst these may be mentioned the deterioration of hospital premises during the war, the shortage of building materials, which is likely to continue until vast arrears of housing are made good, and the acute shortage of nurses. Whilst the last has affected the children's nursing service less than it has some other branches, e.g., the nursing of tuberculosis, there are nevertheless hospital beds, which are urgently needed, standing empty in most large centers owing to lack of staff. The position in Scotland is most serious with regard to childhood tuberculosis; it is repeatedly found that cases of primary infection in young children have arisen in households where an adult case of phthisis has already been diagnosed but where removal is impossible owing to lack of sanatorium beds. Recent figures show that the over-all incidence of pulmonary tuberculosis in Scotland is rising since the war, instead of showing the postwar fall which might have been hoped for with resumption of more normal conditions. It has also been shown that the incidence of tuberculosis is not closely related to overcrowding, which is perhaps understandable when it is remembered that a small child in close contact with a phthisical parent is likely to become infected whether they are living in five rooms or in one.

NEWS AND ANNOUNCEMENTS

Dr. C. Anderson Aldrich, Rochester, Minn., Director of Child Health Study at the Mayo Clinic, died on Oct. 6, 1949. Dr. Aldrich was a Fellow of the Academy and a member of the Editorial board of PEDIATRICS.

* * *

Dr. Katharine H. Baird, Wauwatosa, Wis., died on Oct. 29, 1949, in Milwaukee of bulbar poliomyelitis. She was a Fellow of the American Academy of Pediatrics.

* * *

Dr. Paul D. White, Chief Medical Advisor to the National Heart Institute of the U.S. Public Health Service, has been named Chairman of the Steering Committee for a National Conference on Cardiovascular Diseases to be held Jan. 18 to 20, 1950, at the Mayflower Hotel, Washington, D.C.

The Conference is jointly sponsored by the National Heart Institute and the American Heart Association. The meeting will be a national conference to bring together physicians, scientists, community service leaders and members of allied professions to formulate a program to combat and control the heart diseases.

* * *

A leading public health administrator, a nurse, and six physicians distinguished for medical research were named as 1949 winners of the annual Lasker Awards of the American Public Health Association.

A special award of $2,500 was made to Dr. Haven Emerson "for extraordinary achievement in developing a program of complete health service in every area of the United States."

The American Academy of Pediatrics was one of two organizations honored for public health promotion "for studies of personnel services and facilities for protection of child health."

The awards have been made annually since 1946 by the Albert and Mary Lasker Foundation for research or other contributions in the fight against those diseases that are the principal causes of death and disability.

* * *

A new health consultation service to states under the auspices of the Children's Bureau was announced on Oct. 21 to State and Territorial health officers.

These five specialists were named as part-time consultants to work with state health officers in the following fields:

Care of premature infants—Dr. Harry H. Gordon, Professor of Pediatrics, University of Colorado. Hearing and speech defects—Dr. William G. Hardy, Director of the Hearing and Speech Center of Johns Hopkins School of Medicine, Baltimore. Cerebral palsy—Dr. Meyer A. Perlstein, Professor of Pediatrics, Cook County Post-Graduate Medical School, Chicago. Child psychiatry—Dr. Grete L. Bibring, Chief of Psychiatric Services, Beth Israel Hospital, Boston. Obstetric care—Dr. John Whiteridge, Jr., Assistant Professor of Obstetrics, Johns Hopkins, Baltimore.

Dr. Leona Baumgartner, Associate Chief of the Children's Bureau, urged that health officials make immediate practical use of child research findings.

* * *

Announcement is made of the organization of the Utah Child Guidance Center which is to be administered under the Departments of Psychiatry and Pediatrics of the University of Utah College of Medicine. Dr. Leonard H. Taboroff has assumed the duties of Director and Assistant Professor in Psychiatry and Pediatrics as of Aug. 29, 1949. He is a diplomate of the American Board of Psychiatry and Neurology and received his training in child psychiatry in the Children's Division (Southard School) of the Menninger Foundation where he was successively a Fellow in Child Psychiatry, School Psychiatrist and Chief of the Outpatient Section.

The staff of the new clinic consists of the following personnel in addition to the Director: two clinical psychologists, two psychiatric social workers, and part-time consultants in pediatric neurology and the convulsive disorders. Stress will be laid on undergraduate and graduate teaching of child psychiatry and integration with the department of pediatrics.

* * *

The Society for Pediatric Research announces that during the academic year 1948-1949 seven

Mead Johnson Fellows were appointed and have completed a year's postgraduate work. The seven Fellows, the countries from which they came and the institutions in which they have worked are:

Dr. Fabio do Amaral, Brazil—Children's Orthopedic Hospital, Seattle, Wash.

Dr. Hsu Han-Kuang, China—Children's Hospital, University of Cincinnati, and The Phipps Institute, University of Pennsylvania.

Dr. Soledad Manalac-Morales, Phillippine Islands—Pediatric Department, Bellevue Hospital, New York University, New York City.

Dr. M. Vera Buhrman, South Africa—Rochester Child Health Project, Mayo Clinic, Rochester, Minn.

Dr. Alfonso Cardenas, Colombia—Children's Hospital and Department of Pediatrics, University of Louisville, Louisville, Ky.

Dr. Eugenia Rosemberg, Argentina—Harriet Lane Home, Johns Hopkins Hospital, Baltimore, Md.

Dr. Jamil Kheder, Iraq—Children's Hospital, Columbus, Ohio.

* * *

The Long Beach Pediatric Society was organized in January 1949. Programs at the monthly meetings have included journal reports and addresses by authorities in fields of medicine related to pediatrics.

Only physicians who have completed the hospital training required by the American Board of Pediatrics are eligible for election to associate membership in the society. Full membership is automatic upon acceptance of an associate member by the American Board of Pediatrics. Only full members are eligible for the offices of president and vice president.

Officers of the society are: H. Milton Van Dyke, President; George O. Boucher, Vice President; William G. Zantiny, Secretary-Treasurer.

* * *

Dr. Robert S. Strong, Pass Christian, Miss., an Emeritus Fellow of the Academy and formerly Professor of Pediatrics at Tulane University, New Orleans, La., has been placed on the Army of the United States Retired List in the grade of colonel on June 29, 1948. He was eligible for such benefits by reason of age and satisfactory military service over a period of 32 years on active duty and on the reserve list.

* * *

Dr. Lawrence B. Slobody is the newly appointed director of the Department of Pediatrics, New York Medical College, Flower and Fifth Avenue Hospitals, New York, N.Y. He has been acting director of the department and attendant pediatrician at Flower and Fifth Avenue Hospitals and of the Metropolitan Hospital at Welfare Island. He is also chief of the Frederick S. Wheeler Laboratory for Nutritional Research.

* * *

The Academy of Pediatrics has announced that Dr. John B. Griggs has replaced Dr. J. Harold Root as State Chairman for the State of Connecticut.

* * *

The following candidates were certified by the American Board of Pediatrics:

CLEVELAND, OHIO—SEPT. 16, 17, AND 18, 1949

Anderson, Oscar William, 1301 Columbia St., Seattle 4, Wash.
Anderson, Warren Rouvel, 600 Northwest Security Bank Bldg., Sioux Falls, S.D.
Block, Walter M., 809 Higley Bldg., Cedar Rapids, Iowa
Boyette, Dan P., Kinston Clinic, Kinston, N.C.
Camp, Raymond S., 505 W. University Ave., Gainesville, Fla.
Chinnock, Robert Fisher, 312 N. Boyle Ave., Los Angeles, Calif.
Coursin, David Baird, 37 W. Orange St., Lancaster, Pa.
Defoe, Edward Carl, Jr., 319 Fulton Fresno Bldg., Fresno, Calif.
DiLorenzo, S. Francis, 195 Grove St., Waterbury, Conn.
Everist, Bruce Ward, Jr., Green Clinic, Ruston, La.
Feldman, Felix, 154 Woodruff Ave., Brooklyn 25, N.Y.
Fisher, Alexander Sand, 204-5 Little Bldg., E. Liverpool, Ohio
Goldstein, Harold M., 50 W. 96th St., New York 25, N.Y.

Glaser, William, 1098 Chapel St., New Haven, Conn.
Govan, Clifton Dancy, Jr., 3705 E. Colfax, Denver, Colo.
Gross, Esther S., 202 F. South Temple, Salt Lake City, Utah
Heavenrich, Robert M., 529 W. Genesee Ave., Saginaw, Mich.
Hedrick, Philip William, 654 E. 54th St., Indianapolis, Ind.
Heskett, Robert Glynn, Medical Center Bldg., Spokane 9, Wash.
Hill, J. Richard, 3343 Fourth Ave., San Diego, Calif.
Hirschl, Daniel, 1745 President St., Brooklyn 10, N.Y.
Jackson, Logan Edward, 302 Cherry Ave., Long Beach, Calif.
LaCour, Bennett Joseph, Jr., 506 N. Third St., Monroe, La.
Lagozzino, Daniel A., 4827 Delaware Ave., Everett, Wash.
Lang, H. Bickford, 815 Raspberry St., Erie, Pa.
Lanier, James Cureton, Jr., 208 Nasrallah Bldg., 2720 Park St., Jacksonville, Fla.
Larson, John B., 223 W. Woodlawn Ave., Louisville, Ky.
Leaton, Robert Edward, 3102 San Jacinto, Houston 4, Texas
Lindblade, Victor Y., 3339 Fourth Ave., San Diego, Calif.
Lowrey, George H., University Hospital, Ann Arbor, Mich.
Mautner, Hans, Wrentham State School, Wrentham, Mass.
May, John Arthur, Medical Arts Bldg., Portland 5, Ore.
Meizlik, Edward H., 225 Eighth Ave., McKeesport, Pa.
Mercer, Robert Dean, Babies and Children's Hospital, 2065 Adelbert Rd., Cleveland, Ohio
Michaels, Bernard Irvin, 3500 Fifth Ave., Pittsburgh 13, Pa.
Moore, Henry Woodbury, 1412 Bull St., Columbia, S.C.
Neils, Julius K., 202 Fine Arts Bldg., Bellingham, Wash.
Nielson, Harriet West, 109-A N. Richmond Road, China Lake, Calif.
Ostergard, Robert Preston, 184 Washington, N.E., Warren, Ohio
Panos, Theodore Constantine, Children's Hospital, Galveston, Texas
Perry, Thomas Lockwood, Jr., 4614 Sunset Blvd., Los Angeles 27, Calif.
Prince, George Edward, 311 Realty Bldg., Gastonia, N.C.
Ramsey, Joseph Hawthorne, Norwood Clinic, 1529 N. 25th St., Birmingham, Ala
Reardon, Frederick, Jr., 713 E. Market St., York, Pa.
Ruby, Arthur L., 1331 E. 19th St., Brooklyn 30, N.Y.
Saunders, Allen, 820 Catherine St., Ann Arbor, Mich.
Shuller, Thurman, McAlester Clinic, McAlester, Okla.
Solow, Irwin A., Medical Arts Bldg., Pittsburgh, Pa.
Stine, Frederick A., 1124 Carew Tower, Cincinnati, Ohio
Stovall, Virginia Sugg, 1101 South Texas Bldg., San Antonio, Texas
Thomas, Orville C., 1836 Line Ave., Shreveport, La.
Traggis, Demetrius G., Dept. of Pediatrics, University Hospital, Ann Arbor, Mich.
Troy, Jack M., 1900 Indianapolis Blvd., Whiting, Ind.
Tunick, Frederick L., 1776 Union St., Brooklyn 13, N.Y.
Weick, George E., 809 N. Seventh St., Boise, Ida.

BROOKLYN, N.Y.—OCT. 21, 22 AND 23, 1949

Beloff, Jerome Seymour, 213 E. Main St., Meriden, Conn.
Benson, Thomas D., 4210 St. Paul Blvd., Rochester, N.Y.
Borow, Sydney, 3400 St. Vincent St., Philadelphia 24, Pa.
Briscoe, Philip, 212 Prince George, Annapolis, Md.
Castiglione, John Brandon, 222 W. Willow St., Visalia, Calif.
Cohen, Albert, 299 Broadway, Cambridge, Mass.
Duncan, Peter Alexander, 264 King St., Port Chester, N.Y.
Elmore, Samuel E., Jr., 157 Pine St., Spartanburg, S.C.
Finck, Harold Y., 2912 Naylor Rd., S.E., Washington, D.C.
Harwin, Martin, 65 Lenox Rd., Brooklyn 26, N.Y.
Hertzmark, Frederic, 976 Blue Hill Ave., Dorchester 24, Mass.
Jacobs, Martin H., 96-14 63rd Drive, Forest Hills, N.Y.

Kibee, Frank W., Lincolnville, Me.
Koenigstein, Robert, Sea View Hospital, Staten Island, N.Y.
Koweity, Steven Ellis, 100 Madison Ave., Franklin Square, L.I., N.Y.
Lawrence, Margaret Morgan, 33-11 107th St., Corona, N.Y.
Leyva, Fernando R., 1832 K St., N.W., Washington, D.C.
Lipscomb, Laura L., 663 W. Peachtree St., N.E., Atlanta, Ga.
Lubenstein, Herman, 1585 White Plains Rd., Bronx, N.Y.
Medoff, Harold S., Hosp. of the Univ. of Pa., Philadelphia, Pa.
Monagan, Thomas M., 195 Grove St., Waterbury, Conn.
Nelson, Irving, 150 E. Hartsdale Ave., Hartsdale, N.Y.
Nicosia, Arnold Paul, 348 Park Ave., Munsey Park, Manhasset, L.I., N.Y.
Palmer, George Saxon, 110 S. Duval St., Tallahassee, Fla.
Payton, Charles Frank, 611½ S. Washington, Royal Oak, Mich.
Perillo, Louis Arthur, 638 Amboy Ave., Perth Amboy, N.J.
Piserchia, Gerald J., 379 Washington Ave., Belleville, N.J.
Randall, Alexander, 133 S. 36th St., Philadelphia, Pa.
Rich, Arthur J., 7945 Riverton Ave., Sun Valley, Calif.
Rich, Homer R., 227 Kiesel Bldg., Ogden, Utah
Robinson, Joseph, 76 W. Union St., Wilkes-Barre, Pa.
Ross, Sydney, 2440 16th St., N.W., Washington 10, D.C.
Ryan, John J., 20 Faneuil Rd., Waltham, Mass.
Sawchuk, Steven, 3701 N. Broad St., Philadelphia 40, Pa.
Scholhamer, Charles Frederick, 116 Avon St., New Haven, Conn.
Shaffer, Frank W., 1451 DeKalb St., Norristown, Pa.
Shipman, Robert Traill, 907 Summit Ave., Jersey City 7, N.J.
Silverstine, Leslie Byron, 53 School St., Bradford, Pa.
Sklar, S. Harvey, 647 Anderson Ave., Cliffside Park, N.J.
Spitalny, Jack M., 225 Lancaster St., Albany, N.Y.
Stiefel, Frederick Harris, 373 Ocean Ave., Brooklyn, N.Y.
Stiller, Ralph S., 1633 Ripon Place, Alexandria, Va.
Stroud, Henry Herbert, 1017 Park Place, Wilmington, Del.
Szelewa, Edward Sydney, 87 Stuyvesant Ave., Newark, N.J.
Thacher, Henry C., 11 Turner St., Auburn, Me.
Varga, Charles, 303 E. 20th St., New York 3, N.Y.
Walke, John T., 503 Washington, S.W., Roanoke, Va.
Weiss, Alvah Marvin, 953 Paulding St., Peekskill, N.Y.
Wood, William Hoge, Jr., 308 E. Market St., Charlottesville, Va.

BOOK REVIEWS

A BABY IS BORN, Milton I. Levine, M.D., and Jean Seligman, New York, Simon & Schuster, Inc., 1949, $1.50, 54 pp.

This 54 page book written by the authors of *Wonder of Life* is another significant contribution to sex education in literature. Material on male and female anatomy, conception, pregnancy, and birth and development of the baby is presented simply, accurately and without sentimentality, and with a feeling of warmth that should make it acceptable both to parents and to children.

Though written for younger children than the pre-adolescents for which *Wonder of Life* is designed, *A Baby Is Born* may well be used in the older age group also. The pediatrician will find this a helpful book for parents, teachers and others who are called upon to answer the questions of young children. Illustrations by Eloise Wilkins are excellent and contribute much to the clarity of the presentation.

NEUROLOGY, ed. 4, Roy R. Grinker, M.D., and Paul C. Bucy, M.D., Charles C Thomas, Publisher, Springfield, Ill., 1949, $12.50, 1138 pp., 416 figures.

The senior author is Director of the Institute for Psychosomatic and Psychiatric Research and Training and Chairman of the Department of Neuropsychiatry of the Michael Reese Hospital, Chicago, Ill. The new junior author is Professor of Neurological Surgery, University of Illinois, Chicago, Ill.

Changes in this extensively revised new edition include the omission of the first few chapters of previous editions. Much of that material has been incorporated in the remaining text. No special treatment of the subject of neurology in young people and children is presented in the text. The subject as presented is reliable and complete with this exception. The book should be a standard text.

MOTIVATION IN HEALTH EDUCATION, The 1947 Health Education Conference of the New York Academy of Medicine, Iago Galdston, M.D., W. W. Bauer, M.D., Lawrence S. Kubie, M.D., Margaret Mead, Ph.D., Foreword by Donald B. Armstrong, M.D., New York, Columbia University Press, 1948, $1.00, 53 pp.

A glance at the list of contributors to this little volume gives some indication of its theme. In place of the usual arguments for more effective health education and academic discussion of how to do it, this is a symposium on fundamental drives and subconscious attitudes which make most people resistant to suggestions about living in a healthful manner. The contributors, two health educators, a psychiatrist and an anthropologist, are admirably qualified for their task, both by training and by their ability to write in an interesting and entertaining fashion. The book is not long and can be read in an hour or more.

All physicians, and pediatricians especially, should be well informed about health instruction, for counseling of patients and parents is a large part of the practice of medicine. This book is highly recommended, not as a manual of teaching methods, but as a stimulus for introspection. After reading it, one cannot help wondering whether his health instruction is meeting the need by really changing human behavior and attitudes about health.

NEW WAYS IN DISCIPLINE, Dorothy Walter Baruch, New York, McGraw-Hill Book Company, Inc., 1949, $3.00, 268 pp.

The author has been a nursery school teacher, experimented with remedial technics in the nursery school, practiced as a consulting psychologist in the field of children's behavior problems and written several books for parents.

The present volume, intended for parents, teachers and physicians, is a colorful discussion of the meaning and management of every-day problems of discipline. With many examples the author makes vivid the frustrations the growing child experiences, especially in his family, and shows how the resultant anger, guilt and suppression are expressed in problem behavior. Throughout the book there are repeated suggestions as to how parents can help the child recognize and express his resentments toward them and others through make-believe and frank talk (not direct action), so that he

can regain his emotional equilibrium and friendliness. These are the well-proved technics of the psychiatrist. The use of such tolerant methods will be difficult for parents to practice because they, unlike the psychiatrist, are a very part of the family tensions which are producing the disciplinary problem.

The book should be useful in broadening the understanding of the physician, nurse, teacher and of those parents who are intelligent, stable and reasonably successful in managing their children. It would probably not be helpful and might be confusing to the troubled parents who are having real disciplinary problems. They need individual psychiatric guidance.

PROGRESS IN ALLERGY, vol. 2, edited by Paul Kallós, New York, Interscience Publishers, Inc., 1949, $7.50, 356 pp.

This second annual review fills a great need and is highly recommended. It is of special value because no other review quite covers the subject matter in this manner.

For example, there is an excellent section on "Immunochemistry" by Kabat of New York. The review on "Allergic Diseases in Animals" by Wittich of Minneapolis shows how universal the allergic phenomenon is in the whole animal kingdom. If the reader is interested in the broad general topic of "Aerosol Therapy of the Lungs and Bronchi," he will find perhaps the most authoritative discussion available, written by one of its pioneers, Abramson of New York. Aerosol therapy, of course, goes beyond the domain of allergy and encompasses a wide range of respiratory infections. Hansel's section on "The Diagnosis and Treatment of Allergy of the Nose" is essential reading. The wide span of material covered is further illustrated by the inclusion of chapters by Kennedy on "Allergy of the Nervous System" and Waldbott on "Bronchoscopic Therapy," among others. Another significant chapter which will arouse a great deal of interest is that on "Allergy in the Middle Ear" by Koch of Stockholm. Such a chapter is important because this phase of allergy is perhaps less well understood than any other. In an extensive article on "Allergy in Diseases of the Skin," Haxthausen of Copenhagen gives an orientation of the European viewpoint in this very difficult problem, which will enlist the interest of pediatricians.

Because of the international scope of these progress reviews under the able editorship of Paul Kallós, the reviewer recommends this series as an excellent addition to medical literature.

PROTEINS AND AMINO ACIDS IN NUTRITION, M. Sahyun, M.A., Ph.D., New York, Reinhold Publishing Corporation, 1948, $7.50, 566 pp.

This is a comprehensive monograph dealing with all aspects of protein metabolism and nutrition in man and lower animal forms. It is composed of 15 chapters on special aspects of the subject written by authors who are well known for their research in the fields dealt with. In addition to basic considerations of protein chemistry, intermediary metabolism and the nutritional essentiality of certain amino acids, the all-important place of protein molecules in the fabrication of such vitally important substances as enzymes, hormones, antigens and immune bodies is clearly delineated.

The practical aspects of the subject are dealt with in special chapters on protein deficiency and its relationship to nutritional anemia, hypoproteinemia, edema, resistance to infection, healing of surgical wounds and so forth. Dr. S. Z. Levine's excellent chapter on protein and amino acid nutrition in pediatrics and in pregnancy should be of special interest to pediatricians and obstetricians.

One of the especially commendable features of the volume is the sizable appendix which contains an extensive table on the percentage composition of American food materials and a supplementary table listing the nutritive value of 100 gm. portions of selected foods. The latter provides data on the water, mineral and vitamin, as well as the protein, fat, carbohydrate and caloric values of the various foods.

GUIDE FOR LOCAL RHEUMATIC FEVER PROGRAMS, New York State Department of Health, Bureau of Maternal and Child Health, Herman E. Hilleboe, M.D., Commissioner, published by Office of Public Health Education, New York State Department of Health, New York City, 1949, 32 pp.

This booklet, prepared under the chairmanship of Edward R. Schlesinger, M.D., Director of the

Bureau, with the assistance of a group of specialized workers, has been reviewed in detail by the Advisory Committee on Rheumatic Fever in the New York State Department of Health. Composition of this Committee includes for the most part important members of the American Heart Association and the booklet has been approved as a guide by the American Council on Rheumatic Fever. The guide outlines and defines general policies, organization of a program, standards for service, acceptance for service or follow-up qualifications and functions of personnel and general procedures which can be recommended.

Its purpose is to set forth patterns for local or state units to follow for organization and operation of a composite, coordinated health program and in this instance developed for rheumatic fever control. With proper modification the pattern described can be used elsewhere and anywhere in this rapidly growing field of public health control of a major disease problem, by either voluntary groups or by public health agencies. It is a guide rather than a directive and represents advanced thinking and planning in the field of public health administration.

In Memoriam

ON OCTOBER 6, 1949, Dr. Charles Anderson Aldrich died at his home in Rochester, Minn., aged 61 years, at the peak of a fruition of a long and distinguished career in medicine and pediatrics. He was Director of the Rochester Child Health Institute.

An outline of his activities and interests would extend into every phase of medical practice, for he followed multiple and varied phases in general practice, specialization in pediatrics, clinical investigation, administrative practice, both hospital and community, counseling, extensive committee and conference work, initiating and developing programs and finally pioneering in a community project to study aspects of growth and development of infants and children living in a normal environment and over a long period of time. The development of this program under his guidance is already well under way. He was an author with his wife, Mary M. Aldrich, of two books, *Cultivating the Child's Appetite,* later called *Feeding Our Old Fashioned Children,* and *Babies are Human Beings,* and he wrote many articles. At the time of his death he had in preparation a book on growth and development for publication. It is this subject which was his main interest as one can trace easily and clearly throughout everything he did. It can be said, too, that he, more than anyone else, established philosophies, carried out observations and reached many conclusions which made growth and development a living, meaningful principle in pediatrics. His two books show most clearly of all how these principles and philosophies can be applied to understand simple and fundamental characteristics of infants and children. He was able by his clear thinking and observations to interpret phenomena in child life into full meaning for the rest of us. His final written

word would have placed all this in a form available to those who knew him well and to that outside group to whom that opportunity was not given.

Dr. Aldrich played many important character parts, a major one being his editorial work. First, he joined the editorial staff of the *Journal of Pediatrics* which was inaugurated shortly after the American Academy of Pediatrics was founded in 1931. Second, in 1947 the Academy started publication of its own journal PEDIATRICS under its own control and Dr. Aldrich became a member of the new PEDIATRICS along with the other members of the Editorial Board. He continued with his editorial duties to within a month of his death. Throughout these years he contributed a great deal of his time and ability to establish these two journals. His participation was characteristic of everything he did; it was whole-hearted, unrelenting, active and stimulating.

PEDIATRICS today has felt his influence and it is safe to say that it will continue in a dominant form for years to come. He was unusually able to recognize merit in the material submitted for publication and to recognize character in the individual submitting the manuscript. He was most sympathetic for the younger or the less known author and often pointed out to other members of the Board the full meaning of a message. His opinion and recommendations were rarely questioned; "Whatever Andy says is all right" was a frequent comment. Concurrent with these qualities was his demand for quality, for sincerity, for honesty and for perfection as near as could be attained.

The Editorial Board of PEDIATRICS mourns the loss of a close and dear friend. Recognizing his character and influence, it will be a duty to see that he lives on in the pages to come.

EDITORIAL

THE editorial home of PEDIATRICS during the second year of its existence has been at La Rabida Sanitarium in Chicago. It is a pleasant place to live and work and the progress made this year may be due in part to the spirit which pervades this home. The prospect for the coming years should be bright. The arrangement came about by chance and the course of events.

Christopher Columbus, on his way to France seeking support for his proposed voyage to prove the world was round, stopped for a night's rest at the monastery, Santa Maria La Rábida in Spain. That night he met the Abbot, Juan Perez, and the Andalusian physician, Garcia Fernandez, both of whom approved Columbus' concept and persuaded him to return to Queen Isabella of Spain for aid.

In 1893 the Spanish government built a replica of that monastery for its use at the Columbian Exposition in Chicago. It was situated on a promontory in Jackson Park extending out into Lake Michigan. After the Exposition was over the Spanish Consul in Chicago, acting for his government, presented the building to a group of ladies of Chicago who joined together to use it for the care of sick infants and children during the summer months. This care eventually included older children and finally those suffering from rheumatic fever. The original building was destroyed by fire and in 1931 the present building was built, the care of the children was extended to the year round, and only children convalescent from rheumatic fever were admitted.

In 1945 a reorganization of the hospital took place with three main features concerned: first, the control was placed in a men's board of trustees; second, cases of rheumatic fever during the active stages only were admitted, and third, the hospital was affiliated for professional services with the medical schools of Chicago. The deans of these schools, in association with other professional schools in the universities and especially through the departments of pediatrics in the medical schools, now determine principles and policies to be carried out by the Chief-of-Staff in the fields of medical care, education and research. About 80 children are accommodated daily in the hospital. Opportunities for research and education are available at the hospital to physicians, nurses, medical social workers, occupational therapists, nutritionists and other professional workers interested in rheumatic fever. There is also close affiliation with the Council on Rheumatic Fever of the Chicago Heart Association. The Editor of PEDIATRICS is Chief-of-Staff of La Rabida Sanitarium and also Medical Director of the Council on Rheumatic Fever.

The Editorial Board of PEDIATRICS is deeply appreciative of the opportunity to be "at home" at La Rabida Sanitarium. We thought readers of PEDIATRICS would be interested in knowing about La Rabida Sanitarium. The spirit of leadership and crusading may be seen in PEDIATRICS and the American Academy of Pediatrics which supports it.

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